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EDITORIAL

Two years ago we commented on the use of cortisone in syphilitic eye disease (Editorial, March, 1953) and simultaneously presented an important paper by Ashworth (1953) reporting his experience in Manchester In addition, the discussion which followed Ashworth's address to the Medical Society for the Study of Venereal Diseases on November 28, 1952, indicated the early impressions obtained by other venereologists in Great Britain On page 9 of the current issue Dr G O Horne, of Leeds, reviews the present position of topical cortisone in syphilitic interstitial keratitis and reports his own experience in 23 patients The view that topical cortisone is now the essential adjunct to systemic antisyphilitic treatment in these cases of interstitial keratitis is widely held throughout Great Britain, and its increasingly recognized value in this condition is in marked contrast to the recession of enthusiasm which has resulted from further experience of systemic cortisone and ACTH in other diseases, notably rheumatoid arthritis For maximum benefit, local cortisone must be used in the earliest stages of syphilitic interstitial keratitis, and we would again emphasize the importance and value of close cooperation between venereologist and ophthalmologist in the management of such patients The wider use of the slit-lamp microscope in the early diagnosis and control of treatment of these cases will be stimulated by the valuable article on this subject by Dunlop and Zwink (1954)

In December, 1954, we regretfully bade farewell to the *American Journal of Syphilis, Gonorrhea and Venereal Diseases* We now welcome the first issue (January, 1955) of *The Central African Journal of Medicine* * from the new State of the Federation of Rhodesia and Nyasaland Medical men in the heart of tropical Africa are relatively few and far between and professional isolation is one of their hardships This new journal can help local practitioners to keep in touch not only with medical work in other continents but also with that of their colleagues throughout Central Africa For success, the Journal must be actively supported by those it is intended to serve, and there is no doubt that observations reported from their daily work throughout the new Federation can be of interest to readers outside Africa This is especially true of the treponematoses and venereal diseases, and we look forward to articles on these conditions in *The Central African Journal of Medicine* David Livingstone was probably the first medical man to practise in Central Africa and has many claims to be regarded as the founder of this State It is appropriate, therefore, that his statue should be chosen as the emblem on the cover of the new journal Besides being an explorer and missionary Livingstone was no mean clinician and his observations of a century ago on the epidemiology of syphilis and his appreciation of the venereal and non-venereal forms of treponematosis are of great interest to the modern venereologist If the spirit of Livingstone lives on in the doctors of the new Federation, the success of *The Central African Journal of Medicine* is assured

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* Published bi monthly P O Box 2073 Salisbury S Rhodesia

NORWAY CONQUERS VENEREAL DISEASES*

BY

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In many parts of the world venereal infections still offer a major threat to marriage, family life, and reproduction They remain a threat even in Norway, where the sharp rise in incidence when the pre-war control programme was sabotaged during the Nazi occupation bears witness to the need for constant vigilance, especially in a maritime nation

Norway abolished legalized prostitution in 1887 (Hovde, 1943), and about 1902 a comprehensive Bill for the control of infected prostitutes was rejected in Parliament lest it re-introduce recognized and regulated prostitution In 1923, a new proposal was rejected by the Department of Social Affairs, but certain measures were introduced piecemeal before World War II for the care of sailors, especially in the seaport towns

Paradoxes came with the Nazi occupation For example, the official Nazi code for public morals was patriarchal, anti-feminist, anti-abortionist, and anti-contraceptionist, and was not unlike that of Norway s pious mission groups which were permitted to meet during the Occupation The Nazis closed the Oslo birth control clinic, falsely accusing it of abortionist practices They seized Max Hodann's books in certain public libraries, and published their own version of the doctrine of race hygiene (Fuglesang, 1944), which, in its turn, was promptly expunged from Norwegian libraries after the war The Germans were forbidden to report cases of V D to the Norwegian public health authorities and remained outside the control of the local health officers ‡ There was plenty of paper money, few goods, and some of the " doom-philosophy " of eat, drink, and be merry ! Some fraternization with Norwegian girls occurred and some of their offspring now present adjustment problems in the Oslo schools As in all war areas, the incidence of V D rose sharply in Norway during the occupation

After the Liberation, under an ordinance dated June, 12, 1945, between 2,000 and 3,000 infectious cases were quarantined in a colony This ordinance expired in October, 1946, and was followed by the law of December 12, 1947, which provided for team work by public health and police authorities, protective agencies, and institutions, and for public education in physical sex hygiene

Historically, the connexion between general sex education and the public health campaign against venereal diseases preceded the war, and was carried on as a public health programme, not combined, as in the U S A , with a programme of sex education in terms of moral purity or of positive psycho-social goals and rewards It is true that Norway's world-famous health director, Karl Evang, first made his reputation as editor of a periodical (Evang, 1935) which crusaded both against venereal disease and against general sex ignorance and taboos This work stemmed from the overwhelming question-mail that poured in upon him in response to a health-column he wrote for a popular newspaper It is also true that the extremists of the opposition attribute the recent sex education programme of the Church and Education Department to Evang, whose bureau is part of the Department of Social Affairs But I was assured in various quarters that his influence was very indirect and general Since World War II there has been no extensive *general* sex education as we know it, and the gains in venereal disease control cannot be attributed to this The 1947 campaign of the Norwegian People s Aid (*Norske Folkehjelp*) for enlightening the public on the physical menace of V D (Helsedirektøren, Oslo, 1946a, b, 1947) was stimulated by the post-war increase and by the widespread ignorance§ revealed by Gallup Polls Of those

* [illegible] for publication on June 9 1954

† [illegible] ofessor in Norway

‡ [illegible] rities forbade German citizens to go to Norwegian physicians for the treatment of V D This had a bad effect as many Germans were afraid to visit their own doctors for fear of degradation or spoiling their chances of advancement (H C Gjessing personal communication 1954)

§ In Sweden by contrast (in April 1946) 94 per cent knew that they must do something if a venereal disease infection is suspected 52 per cent believed syphilis curable while 40 per cent did not know

questioned, 85 per cent favoured sex education in the grammar schools (Rummelhoff, 1949) Since 1948 the public have been persuaded (Helsedirektoratet, 1948) to accept the enforcement of that combination of compulsory reporting, follow-up of sources, and practically free* but compulsory penicillin treatment, to which the startling reduction of civilian V D rates in Norway is attributed by Dr H C Gjessing, who heads the V D Division of the Oslo Board of Health (Gjessing, n d , 1945, 1949, 1951) Of the combined factors, the free issue of penicillin since 1946 to the physicians by the chemists, who are state-reimbursed on requisition, is considered to be the most important

Cases of venereal disease are not reported by name,† but since 1948 a special report on other details including sources of infection has been required for each case, and the physicians are said to cooperate fully The name is given only if treatment is neglected or refused and active legal compulsion is required Cases are summarized by the local health authorities and reported to the National Department of Social Affairs No spot-maps are kept, but sources of infection are charted The only effective sanction for the revealing of sources of infection is the threat of non-treatment at the public clinic Some infections, especially old cases in the later stages, are being found and reported through the increased practice instituted by employers of routine physical inspection for factory jobs, which is often repeated annually ‡

Since "professional" prostitution is prohibited and there are no brothels, the chief sources of infection are girls who have other jobs § They are reported to the police only if they do not attend for treatment when notified, or in Oslo when called on by a nurse Such cases are dealt with by the "Moral Police , consisting largely of women in plain clothes There are no "raids on prostitutes" in the American sense Premises are entered only on responsible complaints of disorder , neighbours seldom complain, and prostitutes are so few that this aspect is of little significance Flagrant disorder is rare No 'lock-hospital" is used , the regular dermatological wards of Oslo's large public hospital suffice when hospitalization is required

Treatment is apparently no longer dreaded by patients ‖ Most local patients go to private physicians, since insurance covers much of the cost Of Oslo's 612 new gonorrhoea cases in 1953, 251 (41 per cent) were diagnosed and treated at the Board of Health Clinic

In Denmark the treatment of venereal diseases has been free and compulsory since 1790, though the new drugs have recently made the programme far more effective The system in other Scandinavian countries seems to have been adopted or adapted from that of Denmark This principle of free but compulsory treatment does not produce concealment, since privacy is safeguarded, and hospitalization is only resorted to for persistent and careless carriers, or for serious degrees of disease The decrease in new cases is comparable to that in Norway, with comparable rises due to the wars ¶

Finland's system of venereal disease control is comparable to that of Denmark, Sweden, and Norway , in Helsinki two venereal disease clinics—one for each sex—provide free treatment (Brunn, 1950)

Incidence in Norway

The rates per 10,000 of population for gonorrhoea and syphilis in Norway (Fig 1, overleaf) show the war-time increase, the post-war peak in 1946, and the rapid decline thereafter The increase in 1946 after the Liberation to above the war-time rate is attributed by some to increased accuracy in reporting, since physicians could only obtain access to the free penicillin treatment by reporting their cases (Strøm and Grette, 1948) Dr Gjessing thinks that the post-war increase was due to improved economic conditions, the effects of which were thereafter offset by penicillin (cf Haustein, 1926) By 1950 the incidence was reduced to 701 new cases of syphilis (of which 426 were in cities), and 2,415 new cases of gonorrhoea (of which 1,711 were in cities) The national rate (1950) for acquired syphilis was 2 1 per 10,000 population that for all venereal diseases was 9 6 per 10,000 ** The number of new cases was reduced by almost one-third in 2 years the *rate* declined by 15 per cent in 5 years The new cases were concentrated heavily in Oslo, with Bergen a lagging second In 1951 the figures were further reduced (Statistisk Arbok, Norge, p 40, 1953) and these gains have been maintained in 1952 and 1953 (Table I, overleaf)

*There is a nominal fee (kr 2) for treatment but since 1911 venereal diseases have been covered by health insurance which embraces all those below a certain income and many (voluntarily) above that level

† Providing the longest series in Europe (since 1884) according to H C Gjessing

‡ The foregoing statements are largely based on interviews with Dr Iversen of the Oslo Board of Health and with Dr Gjessing of the Venereal Division

§ In the post war peak of incidence the Oslo chart shows only infections of Norwegian girls German soldiers had to be treated by German army doctors

‖ Interview with Dr Iversen Oslo Board of Health

¶ Social Denmark (1945–7) pp 218–20 Socialt Tidsskrift Copenhagen

** Sunnhetstilstanden og Medisinal Lovgivning 1950 pp 57 58 147 Statistisk Sentralbyrå 1952

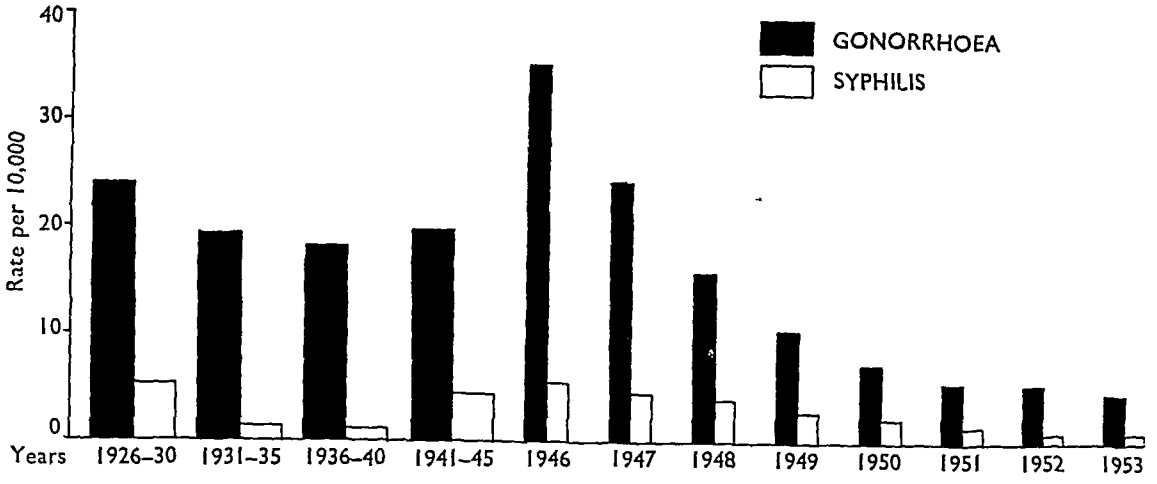

FIG 1 —Rates of gonorrhoea and syphilis per 10 000 population Norway 1926–53

TABLE I

NEW CASES AND RATES PER 10 000 POPULATION NORWAY

Year	Gonorrhoea		Syphilis	
	Cases	Rate	Cases	Rate
1950	2 415	7 5	701	2 1
1951	1,947	5 8	477	1 4
1952	1,946	5 8	304	0 9
1953	1,648	4 9	308	0 9

It was the war and post-war peaks that prompted the campaign of public education and circulation of standard pamphlets against and about venereal infections, by the National and Oslo health authorities, and by the *Norske Folkehjelp* Further publicity is now hardly considered necessary, since the facts are widely known, the peak has been passed, and cure is easy *

Urban Incidence

V D rates in Oslo have been recorded since 1876 (Fig 2, opposite)

Fluctuation has been very marked, with high points in 1882 (120 per 10,000), 1899, 1916, 1925, 1928, 1946 , and low points in 1888, 1907, 1940, 1950 The recent range for gonorrhoea was from *117 per 10,000 population in 1946 to 16 per 10,000 in 1950* , for syphilis it was 27 per 10,000 in 1943, against 3 per 10,000 in 1939 and 1950 † If only primary and secondary cases are included in the rate, as in the U S A , the last figure would be only *1 per 10,000* ‡

It will be noted that Oslo had syphilis well under control before World War II This port of 434,047 people had in 1953 only 675 new cases of venereal disease, comprising gonorrhoea 612 and acquired syphilis 39, as well as 24 cases of late latent and tertiary syphilis § This represents a rate of 14 per 10,000 for gonorrhoea, and of 0 9 per 10,000 for primary and secondary plus early, latent, and congenital syphilis (Gjessing, 1953, 1954) Of the sources of infection, 39 5 per cent were discovered, as against 38 6 per cent in 1949 and 30 7 per cent in 1950 Of local sources, 47 per cent were discovered

In Stavanger, a west-coast port of Norway, the incidence of venereal disease was reported to be high during the war, many persons being infected by the members of the occupying German forces || Now there is no brothel, the few prostitutes are local girls, and there are only eight or ten known carriers The police are brought in only if such girls go aboard the ships ¶ There are perhaps forty new syphilis cases and 130 to 140 new gonorrhoea cases per year, and the problem is under control ** An educational campaign is thought to have contributed to this reduction ††

In Arendal, a southern port, cases are now also few, and infected persons come for treatment

* This opinion is based chiefly on an interview with and reports from Dr H C Gjessing

† Cf letter from Oslo Helserâd January 31 1951 Statistisk Årbok Oslo (Annual)

‡ Beretning om Kjonnssykdommer i Oslo i Året 1950 (mimeo Oslo 1951)

§ Oslo Helserâd 1953 (Annual Report)

|| Venereal diseases have throughout the history of the western nations been blamed on foreign contacts In Oslo in 1952 of 695 new [illegible] per cent and of 75 new cases of syphilis 18 7 [illegible] rigin

¶ [illegible] inspector

** City Physician Stavanger

†† Interview with Dr Jorgen Brommeland Stavanger

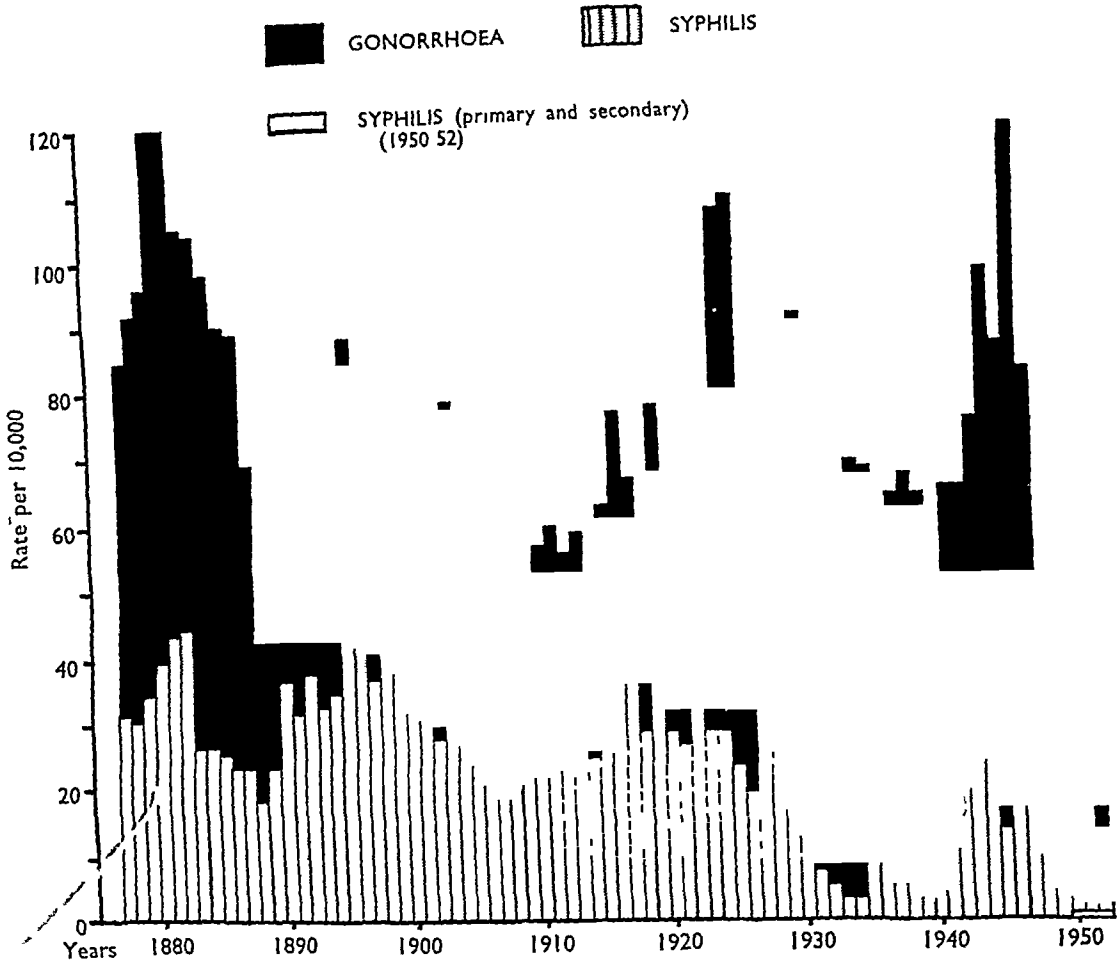

FIG 2.—Rates of gonorrhoea and syphilis per 10,000 population in Oslo, 1876–1953

voluntarily, or on the first warning letter, the police have not yet been invoked *

Rural Incidence

Syphilis rates (primary and secondary) for Norway outside Oslo since 1876 have ranged from one-sixth to one-third of the rates in the capital (Haustein, 1926) The war produced a relative increase in *rural districts* compared with the pre-war ratio Whereas before the war syphilis appeared twice as frequently among males, and gonorrhoea thrice as frequently, during the war gonorrhoea became equally frequent in males and females and syphilis twice as frequent among females as among males

Venereal diseases are now rarer in the rural areas than in the cities In 1950, cases of gonorrhoea in rural Norway were only 42 per cent of those in the urban districts †

* Interview with Dr Knut Egeberg City Physician Arendal
† Sunnhetstilstanden og Medisinal Forholdene 1950 p 147 Statistisk Sentralbyrå 1952

Comparison with Other Scandinavian Countries

Fig 3 (overleaf) presents rates for gonorrhoea and syphilis per 10,000 population for all the Scandinavian countries The syphilis rates are not strictly comparable because of minor variations between the countries in the grouping of different diagnostic stages The rates for Denmark include primary and secondary cases and infections acquired within 12 months The Swedish rates include latent acquired infections of up to 3 years' duration and congenital cases up to 3 years of age, in addition to primary and secondary cases The Norwegian rates represent all patients, including late latent, tertiary, and congenital cases From 1953, however, the Norwegian syphilis rates are calculated only on the basis of primary, secondary, and early latent cases (Gjessing, 1954)

Sweden (Statistisk Årsbok, Sverige, 1953, pp 8, 244) —The rate for syphilis shows a trend similar to that of Norway, but in Sweden there has recently

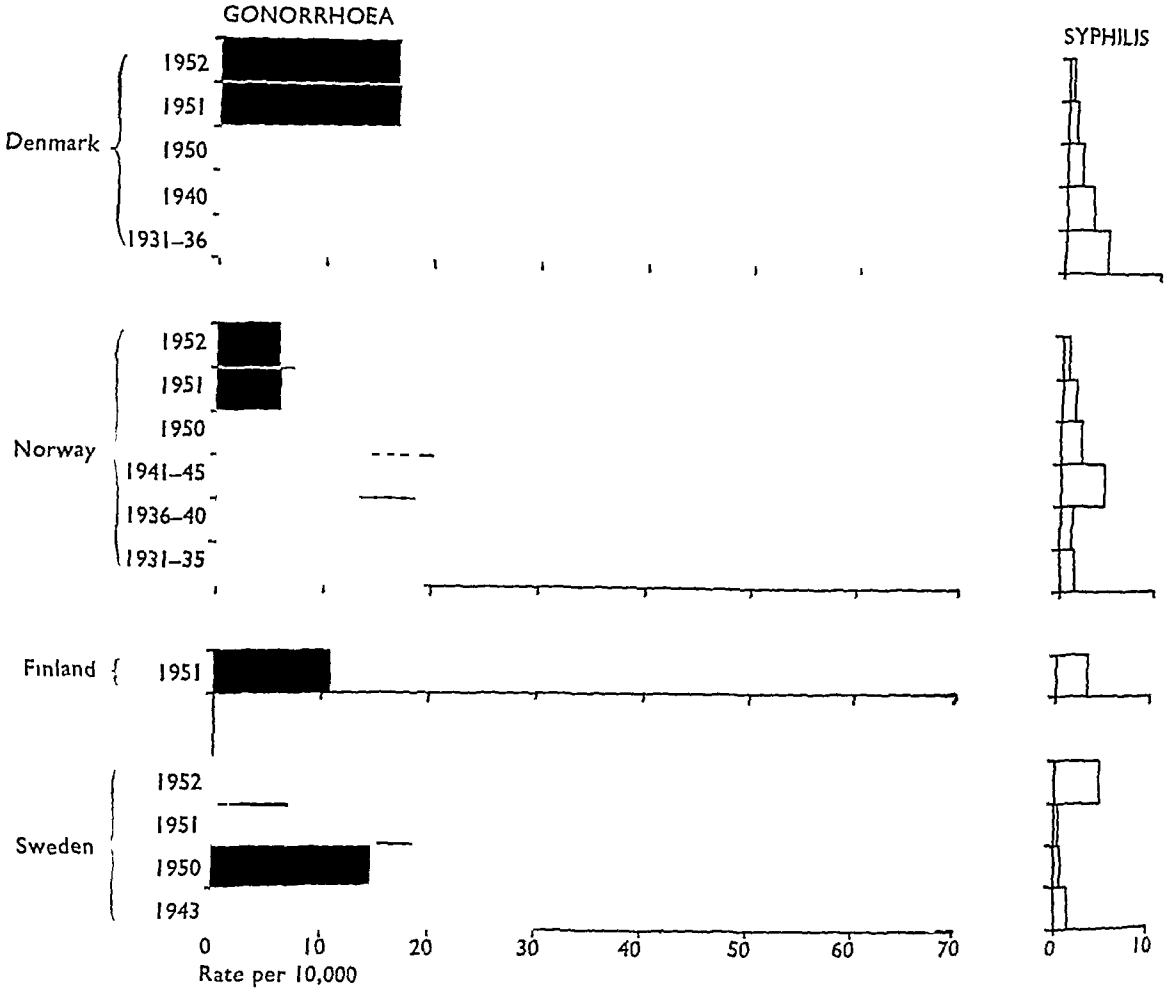

FIG 3.—Rates of gonorrhoea and syphilis per 10,000 population in Scandinavia, selected years

been a slight increase in the rate of gonorrhoea (Table II) The combined rate for syphilis and gonorrhoea is Sweden in 1952 was 21 3 and the increase in the rate for gonorrhoea occurred particularly in persons about 20 years old

TABLE II
VD RATES PER 10 000 POPULATION, SWEDEN

Year	Gonorrhoea	Syphilis
1943	30	1 5
1950	14 5	0 89
1951	18 7	0 67
1952	20 8	0 47

Denmark* (Statistisk Arbog, 1951, p 41, 1953, pp 5, 34)—Venereal disease was well under control before World War II, increased during the occupation, and has since fallen rapidly (Table III)

TABLE III
VD RATES PER 10 000 POPULATION DENMARK

Year	Gonorrhoea	Syphilis
1906–1916 (average)	120–140	40–50
1931–1936 (average)	70	4–5
1940	55	3 (rural 1)
1950	20	1 8
1951	16 4	1
1952	16 3	0 5

Finland (Statistisk Årsbok, 1952, p 60)—The rates for 1951 were 0 32 per 10,000 for syphilis (not

* 'Socialt Tidsskrift' (1945–47) Copenhagen pp 219–20

including tertiary cases), 10 8 for gonorrhoea, and 14 for new cases of venereal diseases Until 1939, Finland's V D rate was higher than Sweden's, but in that year syphilis first fell below 1,000 new cases and gonorrhoea below 12,000 new cases In 1946 syphilis increased to 8,000 and gonorrhoea to 24,000 cases, and the infections were scattered through the country by the demobilized army during this post-war peak But now, as in Norway, V D infection is limited almost exclusively to the seaports, 1950 showed only 400 new syphilis cases and 5,000 new gonorrhoea cases

Venereal Disease and the Army

Prophylaxis specifically for the prevention of venereal diseases has been available to civilians in Norway through several channels, including commercial sales and physicians' prescription Advertising is legally forbidden, but proceeds by transparent euphemisms, such as "hygienic articles" Prophylaxis became a public issue only in relation to army practices,* and especially in regard to Norway's so-called "Germany Brigade", the token occupation force kept in the British Zone of Germany until 1953 Dr H C Gjessing's reports show that practically all the new cases of V D brought into Norway since the war, apart from those involving sailors in the ports, came from the "Germany Brigade" It was a self-defeating price to pay for a symbol of victory, national pride, and official morality!

The post-war increase in the incidence of both civilian and military venereal disease created an emergency Enlisted men found infected were turned over to civil health authorities, and the tests gave only 0 14 per cent positive reactions † Welfare work, recreation, and propaganda were increased, but their effectiveness was discounted by the army physicians

It is interesting to note that prophylaxis has been and is compulsory for merchant seamen,‡ an important group in the Norwegian labour force, without apparent objection from religious groups, some of which maintain elaborate social services for sailors on board and in ports, even overseas Prophylactic packets had been issued free to the army during the war and the practice was continued in Norway in the first year after the war But in 1946 strong opposition arose from various religious groups

Because of the public controversy, the Defence Department set up a special committee in 1946 This military committee represented the army medical corps, the three defence branches, the chaplains, the welfare organizations, and the health directorate Before July, 1947, a small informal committee met to organize the opposition Lutheran leaders headed by Bjarne Hareide launched a giant petition of protest, supported by religious and conservative groups, claiming that the standardizing of prophylactic procedures would indicate official acceptance if not endorsement of extra-marital indulgence The petition circulated through organizations and individuals, and was supported by 442,000 people The argument was not presented on legal grounds It was claimed that whereas soldiers had hitherto been individually free to purchase prophylactics, official recognition of their use would seem to offer an assurance, an advertisement, an encouragement to indulgence, objectionable to Christian morality § This claim that the army procedure would lead some boys into sexual intercourse who would not otherwise be corrupted was partly countered by the findings of a voluntary questionnaire answered by 421 of 423 recruits of 20 to 21 years of age, 82 2 per cent of whom had previously had intercourse ‖ 71 7 per cent before the age of 19, the year of conscription, and 36 per cent at the age of 16 On November 20, 1947, the report from the military committee (No 204, 1945/46) was approved unanimously except for the section on the routine issue of packets, but this section was also passed in Parliament by 76 to 45 votes The Defence Department continued the practice until 1948, but packets have since been issued only on personal application to the health corporal, who was to keep no list, but to report to the divisional medical officer if any one soldier requested so many that re-sales were suspected Despite dissent on the issue of packets, there was unanimous approval of setting up prophylactic stations, but this was done for the "Germany Brigade" only The army also traced the sources of infection in 52 per cent of the cases, a larger percentage than that obtained in civilian medical practice Sources and soldiers discharged uncured continued to be reported to the civilian health authorities A study of 113 infected cases showed that 99 (88 per cent) had not used condoms, and that in three of the remaining 14 the condom had broken Without information on the number of exposures without preventives *and* without infection, there is no proof of the effect of condoms,

* Cf Forhandlinger i Stortinget No 164 p 146, July 10 Interpellation from Ramndal (Liberal) on the moral level among the soldiers General debate Hauge replying

† U S white recruits 1940–42 showed 1 per cent positive at 20–25 years of age

‡ Interview with Dr Iversen Oslo Board of Health

§ The foregoing account is based upon an interview with Dr Bjarne Hareide director of the Institute for Christian Propaganda

‖ A similar study in Sweden gave 81 per cent Studies of students showed much lower rates 58 per cent and 36 per cent

but the rates of infection diminished with their use

As late as 1952 the newspapers carried front-page stories with such headings as " Norwegian Soldiers' Intercourse with German Girls Statistically Revealed " The many cases of venereal disease were said to be due to drink and to neglect of preventives According to Berdal (1950), 42 per cent of the soldiers in the latest brigade had intercourse in Germany There were 202 new cases of syphilis and 646 new cases of gonorrhoea among 22,000 Norwegians in Germany in $2\frac{1}{2}$ years In 6 months, one brigade had a syphilis rate (14 per 1,000) seven times that in the home divisions During 6 months of 1949, the rate was 4 1, but in 10,000 men in the home divisions not a single case was reported In the same period the gonorrhoea rate for the " Germany Brigade " was thirteen times the rate for the home divisions, which was almost down to the civilian level For some reason sergeants' rates were six or seven times higher than those of private soldiers and officers While 78 per cent of infections occurred in Germany, the rate for those on leave in other continental countries was higher (in one brigade ten times higher) than for those remaining in Germany Of those exposing themselves to risk only 30 per cent of a sample of 2,700 men used condoms The high rates were also attributed in part to the location of the camps, to the largely unchecked increase of V D in post-war Germany, the accessibility of German women, and the use of alcohol The recent reduction of these rates in units serving in Germany was attributed in part to propaganda and instruction There had been no reduction in German civilian rates

These military, religious, and preventive aspects are mentioned here because of the continuing recurrence of war and occupation situations in overseas armed forces, and the factors of public opinion involved in their control So far as Norway is concerned, the withdrawal of the " Germany Brigade " in 1953, and the virtual elimination of venereal disease in Norway, make prophylaxis no longer a public problem—though facilities are still accessible Dr Gjessing considers that penicillin is now so effective against gonorrhoea that there is relatively less need than formerly for prophylactics *

From the present evidence it seems clear that Norway has now protected its families from venereal diseases to the point where even a programme of education for family life (which should of course retain the major facts) needs to lay little stress on the subject as compared with the normal personal, familial, and social aspects of sex

Summary

(1) The development of venereal disease control and certain aspects of public education on venereal diseases in Norway are outlined The interruption of these efforts during World War II is described

(2) The fluctuations in the annual rates for gonorrhoea and syphilis in Norway are presented together with those for the other Scandinavian countries The rapid fall in recent years is particularly noted

(3) The problems of venereal diseases and the use of prophylactic measures in the Norwegian occupation brigade in Germany are described

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* Cf also interview of Dr Mellbye of the National Health Department November 1950

TOPICAL CORTISONE IN SYPHILITIC INTERSTITIAL KERATITIS*

REVIEW OF TWENTY-THREE CASES (29 EYES)

BY

GORDON O HORNE

From the Department of Venereal Diseases, General Infirmary, Leeds

There is still considerable dubiety about the role of cortisone in the treatment of syphilitic interstitial keratitis, and in current practice it is not always used in this condition (or is used in inadequate dosage) although supplies are freely available Among the reasons for this reluctance to use cortisone are the following

(1) *Ignorance of its Value*—This has led to scepticism of good results that have been reported

(2) *Contradictory Verdicts on its Value in the Literature*—Two years ago Woods (presumably representing American opinion) wrote that "syphilologists and ophthalmologists doubt whether cortisone therapy in interstitial keratitis is a justifiable procedure" (Woods, 1952a) Also in America Purnell and Leopold (1952) included syphilitic interstitial keratitis in the list of ocular conditions "not improved" by cortisone Klauder and Meyer (1954) wrote that in the light of their experience they had stopped using cortisone in this condition At a discussion on a paper on this subject read in November, 1952, at a meeting of the Medical Society for the Study of Venereal Diseases, caution was expressed about its value (Ashworth, 1953) Minton (1952) did not include syphilitic interstitial keratitis in a list of conditions "responding favourably" to cortisone On the other hand many apparently excellent results have been reported, for example by Crane and McPherson (1951), Salomaa and Swanljung (1952), Ashworth (1953), Drews, Barton, and Mikkelsen (1953), Oksala (1953), and North (1954)

These contradictory and frequently pessimistic reports on cortisone in interstitial keratitis are probably due to several factors

(*a*) Conclusions drawn from small and unrepresentative series of cases and in particular from its use in some cases in which improvement could not be expected—for example, where there were corneal scars or necrosis (Woods, 1950)

(*b*) Its frequent use in inadequate dosage Excellent immediate results have been obtained even in severe cases when adequate dosage was used, and especially when the patients were hospitalized initially, as in the series of Crane and McPherson (1951), Salomaa and Swanljung (1952), Ashworth (1953), Drews and others (1953), and North (1954)

(*c*) A misunderstanding of what can be expected of cortisone, and in particular the unfair verdict of failure applied when relapses occur after the withdrawal of the hormone (even an attack in the other eye after successful treatment of the first eye has been held against cortisone)

(*d*) Difficulty in interpreting the results of treatment, illustrated by the comment by Lister (1953) that in one of the series of Drews and others (1953) there was a recrudescence a few days after stopping cortisone when it had been used continuously for about 8 months, and that '8 months is an exceptionally long period for one attack This supports Woods s suggestion that cortisone delays or prevents the development of a natural resistance to the disease" In view of the notoriously variable behaviour of interstitial keratitis, a conclusion on the basis of one case is not justified, and, in any event, the recurrence after withdrawal of cortisone might equally well have been a true relapse and not necessarily a continuation of the original attack

(*e*) Premature judgment of the value of cortisone For example, Klauder and Meyer (1954) appear to have condemned the local instillation of cortisone as a result of experience of thirteen patients (21 affected eyes) treated over a period of about 18 months

(3) *Exaggerated Fear of the Side-effects of Cortisone*—Systemically administered cortisone can have undesirable side-effects, but there is no reason to believe on theoretical grounds that it would have any such effects when administered topically to the eyes, and none has been recorded (see especially Steffensen, 1952, Drews and others, 1953) Current topical preparations of the hormone seldom cause local reactions, and irritation attributed to too strong a suspension can be overcome by dilution

* Received for publication September 3 1954

(4) *Repeated Authoritative Warnings by Woods* (1951, 1952a, b) *of Possible Dangers in Syphilitic Interstitial Keratitis* —Woods (1952a) rightly points out that the use of cortisone is potentially dangerous (unless other adequate specific therapy is available) in infections of the cornea resulting from " invasion of the tissues by the exciting micro-organisms " (abscess of the cornea and tuberculosis are cited as examples) In interstitial keratitis, however, there is seldom (if ever) evidence of invading organisms, and the condition has many of the characteristic features of a pure " hypersensitivity " phenomenon In any case penicillin is a very potent spirochaeticide and its use coincidentally would discount any hypothetical danger from cortisone given alone However, the literature already indicates that cortisone can be highly effective in interstitial keratitis (at least judging by immediate results) with or without penicillin (see Drews and others, 1953), and no undesirable local effect has been recorded

Woods's other warning, that prevention of vascularization of the cornea (which he claims is important for healing and for the development of immunity) may result not only in prolonging an attack but in frequent recurrences, can only be finally answered after observations extending over many years Klauder and Meyer (1954) appear to have discarded topical cortisone because they support Woods's views, and interpret their results as meaning that cortisone has a deleterious effect, but there is little other evidence so far to substantiate this view Crane and McPherson (1951) treated seventeen eyes with a 10-day course of topical cortisone, in six of them before vascularization had occurred , in their short observation period they found that only two of the six which had shown no vascularization relapsed, whereas six of the eleven eyes which had shown vascularization did relapse Other authors (including Drews and others, 1953) have had good results even in the very early stages of the disease before vascularization had occurred

The argument of Klauder and Meyer (1954), that the use of cortisone, in their experience, is followed by a high incidence of recurrences, and is objectionable because it involves longer hospitalization and greater expense and incapacitation, can be easily refuted, since even prolonged treatment with topical cortisone is relatively inexpensive and can be carried out at home, and, provided it suppresses the inflammation, does not lead to incapacitation Their alternative method of treatment—artificial fever, thyroid, and possibly testosterone—would appear to be more likely to involve hospitalization, expense, and even incapacitation It can be argued that any number of recurrences (each of which can be promptly controlled by cortisone), but with maintenance of good vision, is preferable to no recurrence at the expense of prolonged distress, vascularization of the cornea, scarring, and permanently impaired vision The iridocyclitis that accompanies interstitial keratitis may also contribute to impaired vision, and this also can be prevented by cortisone

Cortisone has been available for the treatment of syphilitic interstitial keratitis for about 4 years, and whilst, because of the natural history of the disease, it is premature to attempt a final assessment of its value, there would appear to be an indication for a review of the information acquired so far Published reports include a considerable number of small series of cases, and a few larger series Most of these deal only with the more or less immediate effects of cortisone, and there are few reports of observations continued for longer than about a year after the start of treatment

It is the intention here to discuss briefly the following points

(1) the expected effects of cortisone on the natural history of syphilitic interstitial keratitis ,
(2) the practical aspects of its use in this disease ,
(3) the place of systemic antisyphilitic therapy ,
(4) the methods of assessing the effect of cortisone

Experience recorded in the literature will be referred to when relevant to the points discussed Then a report will be given of 23 patients (29 affected eyes) treated between December, 1950, and January, 1954, nearly all of whom are still under observation A brief preliminary report of twenty of these patients has already been published (Horne, 1954a) Finally, conclusions will be drawn as to the role of cortisone and the best way of using it in the treatment of interstitial keratitis

Expected Effects of Cortisone on the Natural History of Interstitial Keratitis

(a) Manifestations of the Attack —Cortisone suppresses the manifestations of inflammation, irrespective of the aetiology, but is particularly effective when the inflammation is of the " hypersensitivity " type It has also been shown experimentally to prevent vascularization of the cornea following various forms of noxious agents Since there is a great deal of evidence that syphilitic interstitial keratitis is an inflammation of the " hypersensitivity " type, and the attacks are self limiting (though of variable duration), cortisone should control the signs and symptoms of this condition The earlier cortisone is started after the onset of inflammation the better would be the result , cortisone has no effect on fibrotic or necrotic tissue

In view of the ready accessibility of the tissues involved, local application of the hormone should be effective Withdrawal of cortisone before the end of the " attack ' (*i e* before the hypersensitivity phase in the cornea had ceased) should be followed by a recurrence of activity Similar effects would be expected in the iridocyclitis that frequently accompanies interstitial keratitis All these phenomena have been observed to occur

(b) **Duration of Attack** —In view of what is known about the action of cortisone and about the pathology of interstitial keratitis, it is difficult to speculate whether cortisone would have any effect on the duration of an attack (the views of Woods have been referred to), and clinical experience may not elucidate this problem Great variation occurs in individual cases and adequate controls cannot be obtained, since it is not now justifiable to withhold cortisone for this purpose Comparison in this respect with series from pre-cortisone days would be difficult to interpret Even comparisons in the same patient in whom one eye was treated in the pre-cortisone days and one treated with cortisone are of limited value, because of the differences known to occur even when two such eyes are treated at different times with the same methods In any case, since cortisone suppresses the manifestations of an attack for so long as it is given, it would be almost impossible to know how long an attack lasted unless the hormone were given in very short interrupted courses

(c) **Incidence of Relapses and Recurrences** —Here also it is difficult to speculate on the effect of cortisone (the views of Woods have been referred to), but it should be borne in mind that the hormone cannot " cure " any disease Comparison with series treated in pre-cortisone days is complicated by the possible influence of differing schedules of systemic antisyphilitic treatment, although the general opinion appears to be that even penicillin has little, if any, more influence on the relapse rate than the chemotherapy which preceded it

Another difficulty in assessing the possible influence of cortisone on the duration of attacks and on the incidence of relapses is that of differentiating between the two In some reported analyses an arbitrary time of freedom from activity (such as a year) was demanded before a relapse was allowed However, if cortisone is used for a considerable period of time with successful suppression of the inflammation, which starts again on withdrawal of cortisone, it may be impossible to be certain whether this is the same attack or a relapse*

* See the comment of Lister (1953) discussed earlier

(d) **Ultimate Visual Acuity** —Permanent impairment of vision after interstitial keratitis results from one or more of the following factors

Opacities and vascularization of the cornea
Corneal dystrophies and changes in its curvature leading to refractive errors
Keratic precipitates
Various sequelae of the accompanying iridocyclitis

If the inflammatory phase can be completely suppressed by cortisone, irreversible tissue changes should be avoidable, and these sequelae should not occur If cortisone is started early and is maintained during the whole of the active stage of the disease, there should be no residual damage to the eye and vision should not be impaired

(e) **Involvement of the Other Eye** —It is difficult to believe that local application of cortisone to one eye could influence the natural history of the disease as it affects the other eye, since the amount used is not adequate to have any systemic effect Confirmation of this, were it needed, is provided by Drews and others (1953) who in some cases used cortisone in alternate eyes when both were involved, and found that there was no effect on the eye not treated , also, in other cases of theirs (and of other authors), the second eye became involved whilst the first eye was under treatment with cortisone Comparison in this respect with series from pre-cortisone days is beset with all the well-known difficulties of such a procedure, some of which have been discussed The literature shows that " the chance of escaping bilateral involvement increases in direct ratio to the lapse of time from the onset of interstitial keratitis in the first eye " (Klauder and Vandoren, 1941) Different series show that if the second eye is to become involved, this will occur within 2 years in between 70 and 95 per cent of cases Opinions differ as to the effect of antisyphilitic treatment on the incidence of involvement of the second eye, but it is worth noting that the American Cooperative Clinical Group (Cole and others, 1937) concluded that " adequate " antisyphilitic treatment, especially if given early in the course of the involvement of the first eye, might have some influence in preventing the involvement of the second eye

Practical Aspects of the Use of Cortisone in Interstitial Keratitis

(a) **Parenteral Administration** —There are about a dozen reports of cases of interstitial keratitis treated with ACTH or parenteral cortisone, but there is no doubt that local administration is the method of choice It is more effective, and the undesirable side-effects of parenteral administration are avoided

(b) **Local Administration**—There has been no adequate assessment of the relative merits of the different methods of local administration of cortisone in interstitial keratitis Most reports have described the results of treatment with drops only Duke-Elder and others (1951) concluded that "in diseases ited to the cornea, the instillation of drops s to be more effective than subconjunctival ctions Drops or ointment, or a combination of seem to be the method of choice" Purnell Leopold (1952) had disappointing results in seven out of eight cases treated with subconjunctival injections Lavery (1952) stated that cases responded to ointment and subconjunctival injections with equal rapidity Drews and others (1953) gained the impression that in two of their cases in which ointment (1 5 per cent) was used the clinical response was less rapid than that produced by the instillation of drops in their other sixteen cases Klauder and Meyer (1954) found subconjunctival injections "of questionable benefit" in their six cases

One possible limitation of topical treatment should be borne in mind Drews and others (1953) described a case (Case 6) in which a patient with severe bilateral interstitial keratitis, with intense photophobia, blepharospasm, and lacrimation, failed to respond in the expected way even after several days of hourly drops, but eventually responded promptly to artificial fever They suggested that the failure of topical treatment may have been due to the intense lacrimation washing away the cortisone

(c) **Time of Administration**—In view of what is known of the pathology of interstitial keratitis and of the mode of action of cortisone, it would be expected that the earlier in the course of the disease it is used, the better the results (the contrary views of Woods have been referred to) This has been the experience of those who have commented on this aspect of the problem (for example, Crane and McPherson, 1951, Duke-Elder and others, 1951) Drews and others (1953) stated that "in several cases treated early in the course of the disease it later became impossible to detect any evidence of interstitial keratitis by slit-lamp examination' Prevention of the development of the characteristic features of interstitial keratitis by the early use of cortisone has a theoretical disadvantage, since it may render more difficult the certain diagnosis of congenital syphilis (an example of a case of this kind has been reported by Horne, 1954b), but this is outweighed by the advantages of the early suppression of the interstitial keratitis

(d) **Cortisone and Hydrocortisone**—Assessment of the respective merits of cortisone (Compound E) and hydrocortisone (Compound F) in ophthalmology is difficult, if only because of the high degree of effectiveness of each of them The general opinion appears to be, however, that in most conditions hydrocortisone is the more effective (Steffensen, Ivy, and Nagle, 1952, Gordon, McLean, and Koteen, 1953, Laval, 1953, McDonald, Leopold, Vogel, and Mulberger, 1953, Gordon, 1954), and it should always be tried if cortisone fails to give good results No information is available on their relative merits in syphilitic interstitial keratitis in particular

(e) **Dosage**—Cortisone does not obey the "all-or-none" rule, and there is clinical and laboratory evidence that its effect is "quantitative"—the more severe the inflammation the greater the concentration required Failure to appreciate this has probably helped to account for the mediocre and poor results reported by some observers Those who have used intensive treatment (hourly or 2-hourly drops), and especially those whose patients were admitted to hospital initially (*i e* where the regular administration of adequate dosage has been ensured), have reported the greatest success (Salomaa and Swanljung, 1952, Ashworth, 1953, Drews and others, 1953, North, 1954)

(f) **Duration of Treatment**—In view of the natural history of interstitial keratitis, with its attacks of unpredictable length, it would be impossible to estimate how long cortisone is required in any particular case Dosage should obviously be maintained at a level intensive enough to control completely all activity of the disease, but it would be difficult to decide, without trial, when to stop cortisone The duration of treatment must therefore be individualized and to a certain extent be empirical, and different authors have applied different principles Ashworth (1953), for example, concluded that "it seems necessary to prolong treatment for at least 3 months' As would be expected, others have had success in some cases with shorter spells of treatment Failure to appreciate this aspect of the problem has probably accounted for the scepticism of some authors

Role of Systemic Antisyphilitic Treatment

It is generally agreed that systemic penicillin has little or no effect on interstitial keratitis, either on the progress of individual attacks or on the incidence of recurrences (see especially Klauder, 1951, Drews and others, 1953) It is premature to draw final conclusions, however, and there is some

evidence (already referred to) that adequate treatment of congenital syphilis does at least reduce the incidence of involvement of the second eye Nevertheless, the treatment of all cases of congenital syphilis, whether interstitial keratitis is present or not, must include the use of penicillin The only problem is whether there is any potential danger in using cortisone without the coincidental " cover " of systemic penicillin The significance of this has already been mentioned, and it has been pointed out that cortisone alone should carry no risk of aggravating the condition Personal experience and records in the literature show that topical cortisone can be given effectively in interstitial keratitis for considerable periods without systemic penicillin, and that recurrences can be adequately controlled by cortisone alone when the initial attack has been treated with cortisone with or without systemic penicillin

Assessment of the Beneficial Effects of Cortisone in Interstitial Keratitis

The effects of cortisone on syphilitic interstitial keratitis and its value in the treatment of this condition can be assessed in terms of immediate and long-term results There is no doubt from experience already recorded in the literature that topical cortisone can have a very beneficial *immediate effect* in interstitial keratitis and accompanying iridocyclitis, the more severe the inflammation the more dramatic the results Subjectively, it completely relieves pain, photophobia, and lacrimation, sometimes within a few hours, and usually within a few days, and impaired vision is rapidly restored This prompt relief of distressing symptoms has important psychological implications, since the long-term effects of prolonged distress (including the fear of blindness) notoriously associated with interstitial keratitis in the past, and aggravated by the youth of the majority of those afflicted, can now be eliminated

Objectively, the evidence of active inflammation usually subsides within a few days, particularly the circumcorneal injection, corneal oedema, and early infiltration, and any accompanying iridocyclitis If dense infiltration and vascularization of the cornea and keratic precipitates have been allowed to develop, these take longer to resolve even in intensively treated cases, and vessels may persist for a long time Cortisone would not be expected to have any effect on established scars or on necrotic tissue Withdrawal of cortisone, as would be expected, is sometimes followed by a recrudescence of the symptoms and signs

Comparison of the immediate effects of cortisone on acute attacks of interstitial keratitis may be difficult to analyse statistically, but the relief of symptoms and suppression of inflammation are so rapid in nearly every case in which adequate dosage is used that strictly comparable series are not required before the conclusion can be drawn that in this respect cortisone is much superior to any method of treatment used hitherto

In the *long-term* assessment the most important criterion is visual acuity Other factors to be considered are, of course, the incidence of recurrences (although, as has been pointed out, this is less important) and the cosmetic appearance of corneal scars In assessing visual acuity, correction for refractive errors must be made, and care must be taken to avoid debiting against interstitial keratitis defects due to choroiditis, since the two frequently co-exist

The final visual acuity offers the most clear-cut method of assessing the relative merits of different types of treatment, although this criterion also is not without its difficulties Results will obviously depend to some extent on the time of the assessment in relation to the onset of the disease If the period is very short the possible effects of later recurrences cannot be considered , but, on the other hand, it is known that some corneal opacities may be slowly absorbed spontaneously over long periods of time, with coincidental improvement in visual acuity

Clinical Investigation

Clinical Material—This comprised 23 patients with syphilitic interstitial keratitis (29 affected eyes) attending the Department of Venereal Diseases, General Infirmary, Leeds, who started treatment with local cortisone between December, 1950, and January, 1954 They remained under observation for periods varying from 6 to 39 months In none was there any doubt about the diagnosis of congenital syphilis, although in one (Case 10) the blood Wassermann reaction was negative Relevant clinical data are summarized in Tables I, II, and III (overleaf) , in the section describing the results of Group D three clinical case histories are included The cases are described as severe, moderately severe, or mild, depending principally on symptoms, severity of involvement of the eye, and visual acuity The age recorded is that at the time of starting cortisone

The limitations of busy routine out-patient departments and lack of cooperation from some of the patients are reflected in occasional deficiencies of information Methods of treatment have necessarily varied as experience has been acquired For various reasons some cases have not been ideally managed, but all of them have been included in the analysis since those which were less well-treated provide useful information During the same period cortisone and ACTH have also been used in the treatment of other types of syphilitic

TABLE I

GROUP A CORTISONE STARTED DURING

Case No	Sex	Age (yrs)	Eye Involved	Duration before Cortisone (wks)	Date Cortisone Started	Clinical Data	Cortisone Dosage (hospital periods in italics)		
							Frequency	Dates	Time (days)
1	M	12	R	3	10 1 51	Severe (C F each eye)	3 hrly	*10 1 51–22 1 51*	13
			L	2		Bilateral iridocyclitis and interstitial keratitis keratic precipitate ++	3 hrly	*15 2 51–7 3 51*	(23) 21
							Three daily	29 3 51–24 4 51	(21) 27
2	F	44	R	6	23 7 51	Moderately severe (C F) Diffuse corneal oedema, no cells in anterior chamber	Three daily 4 hrly Three daily Four daily	*23 7 51–24 7 51* *25 7 51–30 7 51* *31 7 51–4 8 51* *5 8 51–31 10 51*	13 88
3	M	5	R	4½	19 9 51	Moderately severe (P L) Cornea diffusely infiltrated no vascularization keratic precipitates +	Three daily 4-hrly Three daily Five daily	*19 9 51* *20 9 51–24 9 51* *25 9 51* *3 10 51–9 10 51*	7 (7) 7
			L	Few days	19 1 52	Mild Cornea diffusely infiltrated	Ung	19 1 52–8 3 52	50
4	M	13	R	4	2 5 52	Severe bilateral (R —H M L —3/36) Both eyes early vascularization	Five daily Three daily	*2 5 52–10 5 52* *11 5 52–17 5 52*	16
			L	3			Three daily Two daily	18 5 52–24 5 52 25 5 52–31 5 52	14 (8)
							Three daily	9 6 52–21 6 52	13
5	F	29	L	4	28 8 52	Moderately severe (6/36) Diffuse corneal infiltration with vascularization	Three daily	28 8 52–14 10 52	48
*6	M	23	R	Few days	1 10 52	1 10 52 Early interstitial keratitis 15 10 52 Moderately severe (C F) Completely hazy cornea whole thickness oedema tous no vascularization ciliary injection	4 hrly 2 hrly Four daily One daily Four daily 2 hrly (waking hours)	1 10 52–27 10 52 *28 10 52–6 11 52* 7 11 52–21 11 52 22 11 52–20 12 52 21 12 52–3 1 53 21 2 53–16 3 53	27 10 15 29 14 (48) 24
7	M	27	R	Few days	3 8 53	Severe (P L) Completely hazy cornea ciliary injection	2 hrly Hourly Four daily Three daily Two daily	3 8 53–18 8 53 *19 8 53–1 9 53* *2 9 53–1 9 53* 2 9 53–9 9 53 10 9 53–17 9 53	16 3 11 8 8
8	F	7	L	3½	1 10 53	Severe (P L) Dense deep corneal opacity peripheral punctate opacities superficial vascularization at periphery	Hourly Three daily 2 hrly Ung Four daily	*1 10 53–2 10 53* 28 10 53–10 11 53 *11 11 53–3 12 53* 4 12 53–11 2 54 12 2 54–30 4 54	27 14 (6) 17 148
			R	Few days	5 10 53	Ciliary injection small corneal infiltrates no vascularization	As above from 5 10 53		

*See case history *Cortisone Dosage* Drops unless otherwise stated (Ung = ointment) *Visual Acuity* Snellen test types

ocular disease (iridocyclitis in acquired syphilis and choroiditis), but these cases are not reported here

Groups—For convenience of analysis the patients were divided into four groups

Group A, 8 patients (12 eyes)—Cortisone started during first attack of interstitial keratitis (Table I)

Group B, 10 patients (10 eyes)—Previous attack in one eye Cortisone started during first attack in other eye (Table II)

Group C 2 patients (4 eyes)—Cortisone started elsewhere for first attack and continued at Leeds (Table III)

Group D 3 patients (3 eyes)—Cortisone used only for recurrence of previous attacks

Cases 1, 9, and 11 have already been reported (Cases 3, 2, and 4 respectively of Horne 1951)

General Management—The majority of the 23 patients were admitted to hospital for initial treatment with topical cortisone (in Groups A and B three were admitted

FIRST ATTACK OF INTERSTITIAL KERATITIS

Antisyphilitic Treatment			Clinical Response and Sequelae	Most Recent Assessment			
Penicillin (mill units)	Bismuth (g)	Date Penicillin Started in Relation to Cortisone (days)		Time Since Cortisone Started (mths)	Clinical Data	Visual Acuity (unaffected eye in brackets)	
						Right	Left
6	2 2 2 0 1 6	Plus 12	Excellent immediate response 29 3 51 Slit lamp—slight right aqueous flare (promptly controlled by cortisone) No relapse	39	No abnormality seen	6/9	6/6
8	0 2 0 1 8	Minus 4	Good immediate response Corneal infiltration slow in clearing but quite clear when cortisone stopped No relapse	33	Cornea clear, old crenated keratic precipitates	6/12	(6/6)
4	1 0 1 5 1 5	Coincidental	Excellent immediate response No relapse	30	Central cornea clear slight peripheral scarring no keratic precipitates	6/9	
			Excellent immediate response No relapse	26			6/12
8	1 5 1 6 (defaulted)	Plus 5	Excellent immediate response 15 5 52 V A R 6/12 L 6/9 6 6 52 Slit lamp—mild right iritis (promptly controlled by cortisone) No relapse	23	Small superficial nebulae in right cornea only	6/12	6/6
8 5	2 0 1 4 1 0	Plus 15	Good immediate response 9 9 52 Large scattered keratic precipitates patchy infiltration of cornea vessels from limbus No relapse	19	Slight corneal scarring	6/9	(6/12)
8	2 0 2 0 2 0	Plus 27	Temporary improvement then deterioration until admission then excellent immediate response 21 12 52 ? Slight reactivity (controlled by cortisone) 21 2 53 Relapse—central nebula (controlled) No further relapse	18	Small scattered nebulae only	6/6	(6 6)
8	2 0 (defaulted)	Plus 3	Slow immediate response 11 8 53 C F Excellent response after admission 21 8 53 V A 6/9 No relapse	8	No abnormality seen	6/6	(6 6)
8	1 0	Coincidental	Moderate immediate response more rapid when hydrocortisone substituted Recurrence both eyes 17 11 53 (promptly controlled by cortisone)	7	No activity (no other data)	6/12	
			Excellent immediate respon e Recurrence (see above)				6/12

corrected for refractive errors (P L = perception of light only H M = hand movements only C F = counting fingers only)

after cortisone had been in use for 16, 27, and 67 days respectively, and five were treated entirely as out-patients, both of Group C and one of Group D were admitted) Two of the patients who had relapses were re-admitted for further treatment The periods of hospitalization are recorded in Tables I, II, and III (dates in italics), and in the section describing the results in Group D The pupils of the affected eyes were maintained fully dilated with gutt atropine sulphate (1 per cent) and this was continued for variable periods after the control of the inflammation

Cortisone Treatment—The preparation used almost exclusively was a suspension in normal saline of cortisone acetate (5 mg /ml) Hydrocortisone suspension (5 mg /ml), cortisone ointment (15 mg /g), and subconjunctival injections of cortisone (0 25–0 5 ml of a 25 mg /ml suspension) were

TABLE

GROUP B PREVIOUS ATTACK IN ONE EYE CORTISON

Case No	Sex	Age (yrs)	Eye Involved	Duration before Cortisone	Date Cortisone Started	Clinical Data	Cortisone Dosage (hospital periods in italics)		
							Frequency	Dates	Time (days
9	M	27	L	6 weeks	12 1 51	Severe (H M) Extensive interstitial and deep corneal infiltration, gross vascularization no keratic precipitates, dilated iris vessels	3 hrly	*12 1 51–29 1 51*	18
10	M	34	R	8 weeks	20 2 51	Severe (C F) Extensive deep infiltration and vascularization	? Three daily Three daily (intermittent)	20 2 51–27 4 51 *28 4 51–* ? ? –10 3 52	67 1 yr
11	M	17	R	Few days	16 3 51	Moderately severe Patchy corneal opacities deep vascularization keratic precipitates +	3 hrly 3 hrly 3 hrly S I four daily (intermittent)	*16 3 51–29 3 51* *30 4 51–4 5 51* *22 5 51–31 5 51* 3 7 51–17 7 51 18 7 51–23 6 52	14 (27) 9 (17) 10 (32) 1 yr
12	F	28	L	?	5 6 51	Severe (P L) Diffuse corneal oedema ciliary injection	S I four 3 hrly Two daily	*5 6 51–19 6 51* *20 7 51–*?17 7 51 ? 8 51–? 10 51	4 mths
13	M	25	R	8 weeks	27 7 51	Acute interstitial keratitis (no data)	Four daily	21 7 51–8 8 51	19
14	M	11	L	Few days	11 1 52	Severe (C F) Cornea completely hazy	Five daily Three daily	*11 1 52–* 3 1 5 *21 1 52–1 2 52*	13 9
15	F	31	L	1 month	4 2 52	Severe (C F)	Four daily Four daily Three daily Two daily Three weekly	4 2 52–12 2 52 16 2 52–29 2 52 1 3 52–14 3 52 15 3 52–28 3 52 29 3 52–24 10 52	9 (3) 14 14 14 7 mths
16	F	5	L	3 weeks	21 2 52	Severe (C F)	Four daily Three daily Two daily	21 2 52–28 2 52 29 2 52–5 3 52 6 3 52–22 4 52	8 6 48
17	F	14	R	1 month	4 3 52	Severe (C F) Whole cornea infiltrated	Four daily Three daily Two daily One daily	4 3 52–1 4 52 2 4 52–22 4 52 23 4 52–3 6 52 4 6 52–15 7 52	29 21 42 43
18	M	31	R	Few days	6 5 52	Acute interstitial keratitis (no data)	3 hrly Two daily	*( ))–1( ))* 17 5 52–22 5 52	11 6

*See text *Cortisone Dosage* Drops unless otherwise stated (S I = subconjunctival injection) *Visual Acuity* Snellen test types

occasionally used In-patients during the acute stage received one drop in the affected eye (or eyes) at intervals of from 1 to 4 hrs depending mainly on the severity of the condition For the first few days the drops were usually given ' round the clock but as improvement occurred the overnight doses were reduced and eventually omitted One patient (Case 12) was given subconjunctival injections

STARTED DURING FIRST ATTACK IN OTHER EYE

Antisyphilitic Treatment			Clinical Response and Sequelae	Most Recent Assessment			First Eye	
Penicillin (mill units)	Bismuth (g)	Date Penicillin Started in relation to Cortisone (days)		Time since Cortisone Started (mths)	Clinical Data	Visual Acuity	Visual Acuity	Date Involved
4	1 8 (defaulted)	Plus 20	Excellent immediate response 29 1 51 V A 6/9 No relapse	38	Both cornea slight scarring and slight vascularization	6/6	6/6	1950
—	—	—	Slow immediate response Recurrent activity for 1 yr 17 3 51 V A 6/12 16 4 51 C F 4 10 51 V A 6/18 25 2 52 V A 6/9	26	Cornea functionally normal Chorioretinitis involving macula	6/18	No P L (corneal scarring cataract and phako sclerosis)	1935
—	—	—	Excellent immediate response Recurrence of iritis twice (each controlled promptly by cortisone) 3 7 51 Recurrence of corneal oedema Intermittent activity for 1 yr	37	No activity (no other data)	6/6	6/60 (corneal scarring)	1948
—	—	—	Deterioration during subconjunctival injections 13 6 51 } Vascularization progressing 27 6 51 } Improvement on drops in ward then further deterioration Aug 1951 P L only	34	Scattered nebulae only	*P L (feigned)	P L (scattered nebulae and healed chorioretinitis)	1947
—	3 0	—	Good immediate response 1 9 51 V A 6/6 Recurrence about 1 12 51 moderately severe (V A 6/18) deep vascularization (controlled by cortisone) No relapse	32	Scattered nebulae Old keratic precipitates	6/12	6,9	1944
8	(defaulted)	Coincidental	Excellent immediate response 24 1 52 Diffuse patches of infiltration no vascularization keratic precipitates +	27	Corneae clear	6/6	6/6	1948
24 9 6	2 0 2 0 2 0	Minus 18	Good immediate response Acute relapse when cortisone stopped after 9 days (promptly controlled by cortisone) Subsequent supervision inadequate 30 9 53 Diffuse scarring of cornea no further activity	27	Severe corneal scarring	6,24	6 6	?
4 5 4	0 5 0 5 1 0	Plus 35	Good immediate response No further activity after withdrawal of cortisone	25	No activity (no other data)	6 9	6,36 (corneal scarring)	1951
12	1 5	Plus 21	Good immediate response No further activity after withdrawal of cortisone	26	Slight corneal scarring only	6/12	6,60 (corneal scarring)	1951
8	—	Coincidental	Excellent immediate response No relapse	23	Scattered superficial nebulae only	6 6	6 60 (severe corneal scarring)	1941

corrected for refractive errors (P L = perception of light only H M = hand movements only C F = counting fingers only)

initially Cortisone was sometimes stopped for a period before the patient was discharged from hospital, sometimes it was stopped at the time of discharge but usually it was continued on an out-patient basis The preparation, dosage, and duration of treatment used in individual patients are recorded in Tables I, II, and III, and in the section describing the results in Group D

TABLE III

GROUP C CORTISONE STARTED ELSEWHERE FOR FIRST ATTACK AND CONTINUED IN LEEDS

Case No	Sex	Age (yrs)	Eye Involved	Date Cortisone Started	Clinical Data and Treatment	Most Recent Assessment			
						Time since Cortisone Started (mths)	Clinical Data	Visual Acuity	
								Right	Left
19	M	16	Bilateral	March 1952	Interstitial keratitis diagnosed and treatment started elsewhere continued at Leeds (see text and case histories)	24	Both corneae small central nebulae and some deep vascularization Left eye some keratic precipitates	6/6	6/18
20	M	9	Bilateral	November 1952		16	Both eyes few keratic precipitates only	6/12	6/9

Antisyphilitic Treatment—None of Group A had had previous antisyphilitic treatment, all of them were given a course of procaine penicillin (daily injections to a total of 4 to 8 million units), one starting 4 days before cortisone, two coincidentally with cortisone, the rest from 5 to 27 days after cortisone was started, all were subsequently given courses of bismuth (ten weekly injections of a metallic suspension) All of Group B had already had varying amounts of antisyphilitic treatment, six were given penicillin after the involvement of the second eye, and four of these and two others were given bismuth Both of Group C had already had antisyphilitic treatment, one was given further bismuth All of Group D had already had antisyphilitic treatment, one was given further penicillin and bismuth, and another bismuth only

Results

Groups A, B, and C

Immediate Response—In all those patients in Groups A and B (" fresh " cases) who were treated from the beginning in hospital with drops, the immediate response was excellent, being similar to that experienced by other authors using a like dosage, as described above *On the whole, the earlier* in the course of the disease cortisone was started the more rapid were the relief of symptoms, the suppression of activity, and the restoration of normal vision The later cortisone was started, however, the more dramatic were the results Even in cases where there was extensive and dense corneal infiltration and vision was reduced to counting fingers, or less (*e g* Case 8), the cornea cleared completely and vision was quickly restored to normal One patient (Case 12) was initially given four subconjunctival injections at intervals of 3 to 4 days, but failed to improve until drops were started

Seven patients started cortisone drops as out-patients The condition of three of them continued to deteriorate until they were admitted and put on the following schedules

Case 7, 2-hourly for 16 days,
Case 6, 4-hourly for 27 days,
Case 10, less frequently and intermittently for 67 days

All three responded immediately after admission and the institution of high-dosage cortisone The other four were treated entirely as out-patients, the drops being prescribed four times daily at first, and all responded well One (Case 13) had a relapse but it was controlled by further cortisone (out-patient)

Hydrocortisone was used for only one patient (Case 8) the whole cornea was extremely densely infiltrated, and improvement had been relatively slow with cortisone in spite of hourly drops There appeared to be a significantly more rapid improvement when hydrocortisone was substituted, and the cornea eventually cleared completely

The good immediate response occurred irrespective of whether the patients had received or were receiving penicillin, and of when they received penicillin in relation to cortisone (see Tables I and II and case histories) In Case 6 the improvement which followed admission to the ward and increased cortisone dosage coincided with the starting of penicillin

Relapses and Recurrences—The difficulty of interpreting and even of recording, the incidence of relapses and recurrences has already been discussed In two patients an acute relapse occurred as soon as cortisone was stopped prematurely against advice (after 9 days in Case 18 and after 6 weeks in Case 8) Case 13 had an acute relapse 4 months after the end of a course of cortisone as an out-patient (4 drops daily for 19 days) In Case 6 there was a slight symptomless infiltration of the cornea which was discovered 7 weeks after a course lasting 3 months had been stopped (see case history) One patient (Case 11) had two recurrences of iridocyclitis following an initial short course of

cortisone, each of these was promptly controlled by further short courses of cortisone, but there was an acute recurrence of interstitial keratitis a month after the end of the last course, and intermittent activity, requiring further courses of cortisone, persisted for a year In Case 10 intermittent activity also persisted for about a year Courses of cortisone had been given, but the dosage was only moderate or low, and the inflammation was never properly controlled In Case 18, at a review 18 months after starting cortisone, considerable scarring of the cornea was found to have developed asymptomatically There had been a good initial response, but, after adequate dosage for the first 2 months, a very low dosage had been used for a further 7 months

In three patients (Cases 1, 4, and 20) slit-lamp evidence of mild iridocyclitis was discovered shortly after cortisone had been stopped, but in none of them was there any recurrence of activity in the cornea In all these cases the relapses were promptly controlled by cortisone, and no further relapse occurred

The case histories of both patients in Group C are quoted in detail (see Appendix) since they illustrate several interesting aspects of the problem Case 19 had been treated (elsewhere) as an out-patient for acute bilateral interstitial keratitis with only moderate dosage of cortisone, and when the cortisone was stopped, about $3\frac{1}{2}$ months after the onset of symptoms, there was an immediate relapse in one eye This was quickly controlled and vision was restored to normal when high dosage was used in hospital at Leeds A further relapse occurred when cortisone was stopped (against advice) after 5 weeks, but the patient was not seen again until several months later, by which time the whole cornea was opaque, He was re-admitted, and further cortisone controlled the condition, but even after intravenous ACTH the result in this eye was less satisfactory than in most of the other cases This patient had been treated intensively with anti-syphilitic drugs from the onset of interstitial keratitis up to the time of his arrival in Leeds Each of the two relapses was controlled by cortisone without further antisyphilitic treatment apart from one 10-week course of bismuth between the two relapses

Case 20 also had been treated (elsewhere) as an out-patient for acute bilateral interstitial keratitis with moderate or low dosage of cortisone The inflammation had apparently never been satisfactorily controlled, and 15 months after the onset of symptoms both eyes were still actively inflamed After admission to hospital in Leeds and high dosage of cortisone the inflammation was rapidly controlled and vision restored to nearly normal Treatment was stopped after 27 days, and 3 weeks later there was slit-lamp evidence of mild iridocyclitis, which was promptly controlled with further cortisone, but no reactivity of the interstitial keratitis This patient also had received intensive antisyphilitic therapy shortly before the onset, and during the early stages, of the keratitis No further treatment was given after his arrival in Leeds

Involvement of the Second Eye—Of the eight patients in Group A, two had bilateral involvement before cortisone was started In two of the remainder the second eye became involved, a few days (Case 8) and 4 months (Case 3) respectively after treatment of the first eye was begun None of the other four has so far had involvement of the second eye In one of the two patients in Group C there was bilateral involvement before cortisone was started (Case 19), and in the other the second eye became involved about a year after the first (Case 20)

Final Assessment—A special review of all the twenty patients (26 eyes) in Groups A, B, and C was made in March and April, 1954 The examination included biomicroscopy and measurement of the visual acuity (corrected for refractive errors) None of the patients was receiving cortisone at the time of this review The duration of observation after starting cortisone was as follows

Months	6–11	12–23	24–35	36–39
No of Eyes	4	6	12	4

The incidence of relapses and recurrences has already been discussed, the incidence of corneal scarring and the final visual acuity are recorded in Tables I, II, and III In only four of the 26 eyes was the visual acuity worse than 6/12 In Case 12 it has been recorded as " perception of light only ', but in fact her vision was very much better than this There was only very faint corneal scarring through which the retina could be clearly seen and there was no evidence of active or healed choroiditis or of other ocular disease, but the patient would not cooperate for refraction The cornea was perfectly clear when she was discharged from the ward after her initial course of cortisone and the nebulae developed while she was on a very low dosage of cortisone as an out-patient For some reason, not yet elicited, this patient was uncooperative and preferred to feign blindness (there was only perception of light in the other eye as a result of corneal scarring and diffuse healed choroiditis), observations of her actions confirmed that vision could not be much impaired, and was probably in the region of 6/18 or better

In Case 10 (V A 6/18), in spite of the prolonged

TABLE IV
VISUAL ACUITY AFTER TREATMENT
Comparison of present series

Source of Data		*Klauder and Vandoren (1941)	Klauder (1947)		Graham and others (1948)
No of Patients		Not stated	54	59	49 cases
No of Eyes		63	96	97	
Treatment Schedule		Arsenic bismuth artificial fever	Arsenic bismuth artificial fever	Penicillin with or without fever and/or chemo therapy	Arsenic and bismuth some with fever
Time of Assessment		At least 1 yr after starting treatment	About 2½–10 yrs after treatment	1 yr or less after penicillin treatment	Unqualified but probably several years in most cases
Final Visual Acuity (corrected) Percentage Distribution	6/6 or better	31 7 } 55 5	14 0 } 61 5	20 5 } 55 5	53
	6/9 6/12	23 8 }	47 5 }	35 0 }	
	6/15–6/30	31 7	27 5	34 0	37
	Less than 6/30	12 7	11 0	10 5	10

*Visual acuity not corrected in every case †One patient one eye (Case 12) omitted (see text) ‡3 eyes Visual Acuity Case 15 6/24,

activity, the cornea was functionally normal and the impaired vision was almost certainly due to old choroiditis involving the macula

In Cases 19 and 15 (V A 6/18 and 6/24 respectively), the impaired vision was probably due at least in part to corneal scarring The management of both cases had been in some respects unsatisfactory, since corneal opacities were allowed to develop uncontrolled during a period when the patients were not under regular supervision, and when either no cortisone (Case 19) or inadequate dosage (Case 15) was being used The visual acuity in the other eye in each of these patients is 6/6

For the purpose of comparison of this important criterion with other series of cases of interstitial keratitis these results have been summarized (excluding Case 12) in Table IV, which also assembles data adapted from the literature suitable for this purpose The final visual acuity is shown in series treated with what were accepted as the best methods before cortisone was available Table IV also includes two other cortisone-treated series (Oksala, 1953 , North, 1954), with a relatively short observation period In spite of the limitations of the interpretation of data of this type, there is no doubt that cortisone is much superior to all other methods of treatment *

* Table IV confirms the view that penicillin has no advantage over chemotherapy in the treatment of interstitial keratitis judged by the final visual acuity It also suggests that artificial fever therapy believed to be of value did not have any great effect on the final visual acuity although in the only series recorded here in which fever therapy was not used at all a higher proportion of the eyes had a final visual acuity of less than 6 30 Whilst artificial fever would be expected to have a cortisone like effect on interstitial keratitis it is rarely used over long enough periods to control the inflammation completely Indeed if it is true that inadequate dosage of local cortisone has an ultimate deleterious effect (see Discussion opposite) then artificial fever might also have the same effect

For the purpose of comparison, the final visual acuity of the 10 eyes in Group B treated without cortisone is included in Table II

Group D —The three patients in this series had all had bilateral interstitial keratitis previously, and cortisone was used only in the management of recurrences

Case 23, *male, aged* 40, had a severe recurrence in one eye and was admitted to hospital on May 7, 1952 Cortisone drops were given initially five times daily, and the inflammation was rapidly controlled Recurrent activity persisted, and intermittent courses of cortisone were continued on an out-patient basis until February 25, 1953 During this time he was given a course of procaine penicillin (8 million units) and three courses of bismuth (total 8 6 g) There was no further activity, and at a review 23 months after starting cortisone the visual acuity was 6/6

Case 22, *male, aged* 34, had a severe recurrence in one eye and started cortisone (one drop, three times daily as an out-patient) on March 5, 1952 The inflammation was controlled and cortisone stopped on April 24 1952 The patient had a further severe attack in September 1952 (visual acuity, counting fingers only), and restarted cortisone in the same dosage The inflammation was controlled, and cortisone was stopped on *October 6,* 1952 The patient has not attended the hospital since and it is assumed that he has had no further recurrence

Case 21 *male, aged* 25, had a mild recurrence in both eyes and started cortisone (one drop, three times daily) on August 28, 1952 This was continued intermittently until February 23 1953, when there was no slit-lamp evidence of activity The visual acuity (6/18 6'60) was the same as that before the onset of the recurrences treated with cortisone The patient has not attended the hospital since and it is assumed that he has had no further recurrence

OF INTERSTITIAL KERATITIS
with series previously reported

Oksala			North (1954)	†Present Investigation
(1952)	(1953)			
Not stated	24	11	8	19
157	35	18	14	25
Arsenic and bismuth	Penicillin with or without fever	Penicillin fever and topical cortisone	Penicillin with or without bismuth and/or fever and topical cortisone	Penicillin bismuth and topical cortisone
Unqualified but probably many years in most cases	Average 1¾ yrs after treatment	Average 1 yr after treatment	At least 1 yr after starting cortisone	6–39 mths after starting cortisone (see text)
22 3 / 31 8 } 54 1	60	100	79 / 21 } 100	36 / 52 } 88
27 3	26	0	0	‡12
18 5	14	0	0	0

Case 19 6/18—both have corneal scarring Case 10 6 18—cornea functionally normal but healed chorioretinitis involving macula (see text)

In these three cases of recurrences of previous attacks not treated with cortisone, the hormone was also of great value The acute phase was suppressed, and in the two cases in which data are available, loss of vision from recurrent attacks was completely prevented

Discussion

The results of treatment of this series of patients with syphilitic interstitial keratitis conform to the hypothetical discussion in the first part of this paper, and (where comparisons can be made) are as good as, or better than, the experience of most other observers who have used similar methods of treatment Whilst there is no strictly comparable series of cases, treated without cortisone, available, there is no doubt that the results, immediate and long-term, are much superior to what would have been expected without cortisone, and in the cases considered to have been correctly managed, better results could hardly be imagined This conclusion is drawn in spite of the small number of patients, and bearing in mind the notoriously fickle natural history of interstitial keratitis , even without cortisone, good results are sometimes obtained (eventually) in even the most severe cases

The best results were obtained on the whole in those patients who were admitted to hospital for their initial treatment Where the progress and ultimate results were less good this can always be explained by some fault in the management of the case, through lack of cooperation on the part of the patient, inadequate supervision, and inadequate dosage of cortisone, or various combinations of these factors

Since the majority of the patients were given shorter initial courses of cortisone than have been used by others (for example, by Ashworth, 1953, Drews and others, 1953), a relatively high relapse rate might have been expected, but this did not occur This suggests that high initial dosage may tend to shorten the attack There are not enough cases to justify drawing definite conclusions, but this possibility is supported by the observation that the cases in which activity persisted for very long periods (Cases 10, 11, 19, 20) are all those in which moderate or low dosage, or very short courses, had been used initially

The results do not appear to have been influenced by systemic antisyphilitic therapy, except perhaps in relation to involvement of the second eye Whilst in one patient (Case 11) with prolonged activity very little systemic treatment had been given, in others (Cases 19 and 20) there was prolonged activity in spite of intensive treatment in one of the latter (Case 20) activity was controlled and apparently stopped with cortisone without any further systemic treatment being given

Conclusions

From the reports in the literature and the series of 23 cases (29 eyes) reported here it is justifiable to conclude that if topical cortisone therapy is started soon after the onset of interstitial keratitis, and is used in adequate dosage and over a long enough period of time, the patient will obtain prompt relief of symptoms no permanent damage will be done to the eye, and there will be no impairment of visual acuity Even if cortisone is not started until the inflammation has been present for several weeks

and dense infiltration and vascularization have occurred, the cornea can usually be cleared and vision restored to normal or near normal In such cases failure should not be accepted until hydrocortisone (Compound F), and parenteral cortisone or ACTH (or, if these are not available, artificial fever), have been tried There is little evidence to indicate that the use of cortisone in adequate dosage either prolongs an attack of interstitial keratitis or increases the likelihood of relapse On the contrary, in the series reported here, the evidence seems to point the other way Even if it is eventually proved that attacks are prolonged and recurrences more frequent, this is unlikely to be regarded as a contraindication to the use of cortisone Topical cortisone is equally effective in controlling iridocyclitis accompanying interstitial keratitis This form of treatment should now be accepted as imperative

Cortisone should be started as soon as possible, and, ideally, all patients should be admitted to hospital immediately, in order that cortisone may be given under supervision The patients should be kept in hospital at least until all evidence of activity of the disease is controlled, and until normal vision has been restored, though treatment can be given entirely on an out-patient basis if necessary By " adequate " dosage is meant one drop of cortisone suspension 2- or 3-hourly, and even hourly, and " round the clock " if necessary in severe cases Withdrawal of cortisone must necessarily be carried out empirically Provided that the patient can be examined at frequent intervals, trial reduction can be started as soon as all signs of activity of the disease have disappeared, the cornea is clear, and visual acuity restored to normal However, since there is some evidence to show that the ultimate progress may be influenced by the duration of high dosage, this should be continued for several weeks, irrespective of the rapidity of the immediate response There is no evidence that harm can result from using high dosage over a long period of time Indeed, in the series reported here there is some evidence that it is low dosage, without complete control of the inflammation, which tends to prolong the period of activity

After cortisone is stopped, frequent and careful observation must be maintained, since insidious and symptomless relapses may occur, and evidence of iridocyclitis and corneal oedema and infiltration may be apparent only on slit-lamp examination Cortisone should be restarted at the earliest sign of a relapse Indolent infiltration of the cornea and keratic precipitates, if allowed to remain uncontrolled for a long period, may not be cleared by cortisone, and permanent opacity may result Similar principles apply to the management of relapses, whether or not the original attack has been treated with cortisone

There is no adequate evidence on the merits of the different methods of using local cortisone in interstitial keratitis, but it seems that hydrocortisone (Compound F) is superior to cortisone (Compound E) and that drops are the most efficient form of local application, especially in the initial stages of the disease, subconjunctival injections have rarely been as successful, ointment may be useful overnight in the early stages, and for out-patient " maintenance " treatment

Cortisone appears to be equally effective whether or not systemic antisyphilitic therapy is given coincidentally—thus supporting a "hypersensitivity" phenomenon as the pathological basis of the condition Antisyphilitic therapy must, of course, be given

If cortisone is used in the very early stages of a keratitis all evidence of inflammation is rapidly suppressed and the characteristic features of syphilitic interstitial keratitis are not allowed to develop Care must therefore be taken to determine whether or not the patient has congenital syphilis It should be remembered that standard serological tests are sometimes equivocal and even negative in active syphilitic interstitial keratitis, confirmatory evidence of the disease must be sought and family investigations pursued if necessary

Summary

(1) A review has been made of statements in the literature on the value of cortisone in the treatment of syphilitic interstitial keratitis It is obvious that there is still some dubiety about its value An attempt has been made to explain the contradictory reports that have been published, and the persisting reluctance to use cortisone in this condition

(2) A brief discussion has been made of

(*a*) the expected effects of cortisone on the natural history of syphilitic interstitial keratitis,

(*b*) the practical aspects of its use in this disease,

(*c*) the place of systemic antisyphilitic therapy,

(*d*) the methods of assessing the effect of cortisone

Experience recorded in the literature has been referred to when relevant to the points discussed

(3) A detailed report is given of 23 patients (29 affected eyes) with syphilitic interstitial keratitis treated with topical cortisone, and kept under observation for periods ranging from 6 to 39 months after the start of treatment It has been concluded that the correct use of topical cortisone produces

results much superior to all previous methods of treatment

(4) It has been concluded that topical cortisone is imperative in the treatment of syphilitic interstitial keratitis An outline has been given of the best way of using it in this condition in the light of personal and recorded experiences

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APPENDIX

Case Histories

Case 6, male, aged 23, developed interstitial keratitis in the right eye at the end of September, 1952 (Wassermann reaction positive, diagnosis of congenital syphilis confirmed later) In spite of cortisone drops prescribed 4-hourly as an out-patient from October 1, 1952, the condition deteriorated ciliary injection persisted, the whole of the cornea became oedematous, but there was no vascularization, visual acuity was reduced to counting fingers at 1 ft He was admitted on October 28, 1952 Cortisone drops were given 2-hourly until November 7, 1952 (when he was discharged from hospital), and thereafter four times daily until November 21, 1952 By this time the cornea had completely cleared, and visual acuity was 6/9 Cortisone was then reduced to once daily until December 21, 1952, when slight activity was suspected, and the dose increased to four times daily Cortisone was stopped on January 1, 1953, when the cornea was clear again and there was no evidence of activity

A course of procaine penicillin (8 million units) was started on October 27, 1952, and was followed by weekly injections of 0 2 g bismuth The stopping of cortisone on January 3, 1953 coincided with the end of the first course of bismuth (2 g) When the patient returned 6 weeks later on February 21, 1953, he was found to have a large central nebula in the right eye There had been no local symptoms to draw attention to the recrudescence Cortisone was prescribed as an out-patient 2-hourly (during waking hours) for 25 days, until March 16, 1953, when it was stopped The nebula had completely cleared

Two further courses of bismuth (each of 2 g) were given At his last review on March 22, 1954 (18 months after starting cortisone), there was no evidence of any activity in the eye There were a few small scattered nebulae in the cornea and a few faint vessels The visual acuity was 6/6 The left eye has not been involved clinically, and was normal on slit-lamp examination

Case 19, male, aged 16, developed bilateral interstitial keratitis (blood Wassermann reaction positive Hutchinsonian incisors) at the end of March 1952, and was treated at a hospital elsewhere Cortisone had apparently been given initially as subconjunctival injections and the inflammation had been controlled in both eyes Cortisone was continued as drops, but these had been used spasmodically He had also been given a large amount of treatment with penicillin, arsenic and bismuth He moved into the Leeds area, and was first seen here on August 8, 1952 Cortisone had been stopped about 3 weeks previously In the right eye there was a very small nebula no evidence of active disease and the visual acuity (corrected) was 6 6, in the left eye there was severe pain blepharospasm, photophobia, lacri-

mation, circumcorneal injection, and dense infiltration of the whole of the cornea, visual acuity was reduced to counting fingers at 1 ft

He was admitted immediately (August 8, 1952) and cortisone drops were administered 4-hourly round the clock" for 12 days, then twice daily for 12 days The immediate response was excellent, and when he was discharged from the ward on September 1, 1952, the left cornea was clear, and visual acuity (corrected) 6/6 Arrangements were made for his supervision at a clinic elsewhere in the area He was next seen here 7 months later, on March 31, 1953, when the left cornea was found to be completely hazy, and vision reduced to counting fingers at 1 ft Apparently cortisone had been continued for only 2 weeks, but he had attended for ten weekly injections of bismuth There was no pain, photophobia, or lacrimation, and, presumably since the loss of vision had been gradual, he had no complaints In the right eye there was an aqueous flare, but no other evidence of activity

He was re-admitted on April 8, 1953 and cortisone drops were administered to both eyes 2-hourly until May 9, 1953, and then 2-hourly as an out-patient until May 18, 1953 Most of the cornea cleared rapidly, but at the end of this time there was still a fairly dense central infiltrate and visual acuity was only 6/18 He was re-admitted, and between May 19, 1953, and May 27, 1953, he was given four 8-hour intravenous drips, each of 25 mg ACTH in a litre of saline This did not result in any significant local improvement Topical cortisone was restarted (four times daily) and continued until July 22, 1953 At this time there was no evidence of activity in either eye, but there was a small residual nebula in each cornea The visual acuity in the right eye was 6/6, and in the left eye 6/18

At a review on March 27, 1954, visual acuity was still 6/6 in the right eye, and 6/18 in the left There was a small central nebula and some deep vascularization in both eyes, but no evidence of inflammatory activity, some keratic deposits were seen on the back of the nebula in the left eye

Case 20, **male, aged 9,** developed acute interstitial keratitis in October, 1952, whilst under treatment elsewhere for congenital syphilis which had presented as osteitis of the tibia (blood Wassermann reaction positive, Hutchinsonian incisors) He had been treated with cortisone drops as an out-patient, initially 3-hourly for 10 days There had been a good response, but the condition soon relapsed, and, in spite of continued cortisone therapy, had remained more or less active for over a year Apparently the drops had been used only once or twice daily, and probably only intermittently The left eye had become involved about a year after the right one, and had also been treated with only low dosage of cortisone During this time the patient had had a large amount of treatment with penicillin, arsenic, and bismuth

He moved into the Leeds area, and was first seen here on January 25, 1954 The left eye showed deep corneal oedema and infiltration and keratic precipitates, the visual acuity was 6/12 The right eye was also still active, with deep vascularization, the visual acuity was 6/12 The patient was admitted immediately, and cortisone drops prescribed for both eyes 2-hourly until February 5, 1954, and then 4-hourly There was rapid improvement, and by February 11, 1954, there was no evidence of activity, though some residual scarring was present in both corneae Cortisone was stopped on February 21, 1954 On March 23, 1954, there was no activity in the right eye, but in the left eye there was slit-lamp evidence of iritis Cortisone 2-hourly was immediately restarted When it was stopped on April 2, 1954, there was no evidence of activity in either eye, and the visual acuity was 6/12 in the right eye and 6/9 in the left No further antisyphilitic treatment had been given

TREATMENT-RESISTANT SYPHILIS
SHORT REVIEW AND REPORT OF A CASE*

BY

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During four centuries of mercurial treatment of syphilis there has been little documentary evidence of the concept of treatment-resistance in syphilis Mercury, on account of its feeble treponemicidal action, did not interfere to any significant extent with the natural course of infection, and the question of resistance to treatment did not arise In the decade following the introduction of the organic arsenical compounds, Ehrlich's concept of " therapia sterilisans magna " dominated the field, but Ehrlich himself foresaw the problem of drug-fastness in chemotherapy and, recognizing inadequate dosage as its most frequent cause, emphasized the dangers of under-treatment at several international conferences From 1920 to 1940 many reports on treatment-resistant syphilis were published by German and French workers Beerman (1936) lists 430 references Most of these reports discuss resistance to arsenical therapy and some to bismuth

Silberstein (1924) classified treatment-resistance in primary and secondary syphilis as follows

(1) Primary Resistance—resistant from the start
(2) Primary-Secondary Resistance—after initial involution a resistant recurrence develops
(3) Secondary Resistance—arsenical treatment heals the lesions, but after a latent period a resistant recurrence appears

Gougerot (1923, 1931) and Nicolas, Lacassagne, and Froment (1930), cited by Beerman (1936), give a more elaborate classification based on the degree of resistance

(1) Attenuated resistance
(2) Treatment recurrence
(3) True treatment-resistance
  (*a*) primary,
  (*b*) secondary
(4) Treatment activation or stimulation

The increase of treatment-resistant syphilis in the pre-penicillin era was reported almost exclusively from France and Germany, the criteria of resistance being

(*a*) persistence of lesions,
(*b*) persistently positive blood serology tests,
(*c*) persistence of *Treponema pallidum* in spite of adequate treatment, the last being the most reliable

The most common clinical types of treatment-resistant syphilis occur in early infections and are usually cutaneous The lesions may be typical or atypical They are stated to have a predilection for the face, nose, neck, penis, and upper extremities, and are usually atypical at the time of their appearance Precocious tertiarism is present in many of these cases and chancriform recurrences are frequently reported The blood serological reaction tends to be negative more frequently in treatment-resistant early syphilis The host seems to play the key role in treatment-resistance through inability to metabolize the drugs used, failure of defensive powers, endocrine dysfunction, hepatic insufficiency, and so on Clinical evidence supported by *in vitro* laboratory studies suggests that small subcurative doses of a treponemicidal drug and inadequate treatment are more likely to cause treatment-resistance than the quality or brand of the drug used Sometimes resistance may be overcome by changing to another drug

The concept of drug-fast strains of *Treponema pallidum* is discounted by failure to transfer chemo-resistance from a case of treatment-resistant syphilis to rabbits

Before the discovery of penicillin numerous methods of circumventing treatment-resistance were advocated raising the arseno-bismuth dosage, changing the drug and non-specific measures such as injections of liver extract and malarial therapy Only fever therapy gave satisfactory results With the advent of penicillin, however, a safe and effective treatment for early syphilis resistant to arseno-bismuth became available (Nelson and Duncan 1945, Noojin and others 1945 cited by Moore 1947) Although thousands of cases of syphilis have been treated with penicillin during the past decade only one patient with dark-field positive primary syphilis reported by Tyson (1945), cited by Moore (1947) failed to improve with 2 4 mega units penicillin

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mation, circumcorneal injection, and dense infiltration of the whole of the cornea, visual acuity was reduced to counting fingers at 1 ft

He was admitted immediately (August 8, 1952) and cortisone drops were administered 4-hourly 'round the clock" for 12 days, then twice daily for 12 days The immediate response was excellent, and when he was discharged from the ward on September 1, 1952, the left cornea was clear, and visual acuity (corrected) 6/6 Arrangements were made for his supervision at a clinic elsewhere in the area He was next seen here 7 months later, on March 31, 1953, when the left cornea was found to be completely hazy, and vision reduced to counting fingers at 1 ft Apparently cortisone had been continued for only 2 weeks, but he had attended for ten weekly injections of bismuth There was no pain, photophobia, or lacrimation, and, presumably since the loss of vision had been gradual, he had no complaints In the right eye there was an aqueous flare, but no other evidence of activity

He was re-admitted on April 8, 1953, and cortisone drops were administered to both eyes 2-hourly until May 9, 1953, and then 2-hourly as an out-patient until May 18, 1953 Most of the cornea cleared rapidly, but at the end of this time there was still a fairly dense central infiltrate and visual acuity was only 6/18 He was re-admitted, and between May 19, 1953, and May 27, 1953, he was given four 8-hour intravenous drips, each of 25 mg ACTH in a litre of saline This did not result in any significant local improvement Topical cortisone was restarted (four times daily) and continued until July 22, 1953 At this time there was no evidence of activity in either eye, but there was a small residual nebula in each cornea The visual acuity in the right eye was 6/6, and in the left eye 6/18

At a review on March 27, 1954, visual acuity was still 6/6 in the right eye, and 6/18 in the left There was a small central nebula and some deep vascularization in both eyes, but no evidence of inflammatory activity, some keratic deposits were seen on the back of the nebula in the left eye

Case 20, male, aged 9, developed acute interstitial keratitis in October, 1952, whilst under treatment elsewhere for congenital syphilis which had presented as osteitis of the tibia (blood Wassermann reaction positive, Hutchinsonian incisors) He had been treated with cortisone drops as an out-patient, initially 3 hourly for 10 days There had been a good response, but the condition soon relapsed, and, in spite of continued cortisone therapy, had remained more or less active for over a year Apparently the drops had been used only once or twice daily, and probably only intermittently The left eye had become involved about a year after the right one, and had also been treated with only low dosage of cortisone *During this time the patient had had a large amount of* treatment with penicillin, arsenic, and bismuth

He moved into the Leeds area, and was first seen here on January 25, 1954 The left eye showed deep corneal oedema and infiltration and keratic precipitates, the visual acuity was 6/12 The right eye was also still active, with deep vascularization, the visual acuity was 6/12 *The patient was admitted immediately, and* cortisone drops prescribed for both eyes 2-hourly until February 5, 1954, and then 4-hourly There was rapid improvement, and by February 11, 1954, there was no evidence of activity, though some residual scarring was present in both corneae Cortisone was stopped on February 21, 1954 On March 23, 1954, there was no activity in the right eye, but in the left eye there was slit-lamp evidence of iritis Cortisone 2-hourly was immediately restarted When it was stopped on April 2, 1954, there was no evidence of activity in either eye, and the visual acuity was 6/12 in the right eye and 6/9 in the left No further antisyphilitic treatment had been given

TREATMENT-RESISTANT SYPHILIS
SHORT REVIEW AND REPORT OF A CASE*

BY

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During four centuries of mercurial treatment of syphilis there has been little documentary evidence of the concept of treatment-resistance in syphilis Mercury, on account of its feeble treponemicidal action, did not interfere to any significant extent with the natural course of infection, and the question of resistance to treatment did not arise In the decade following the introduction of the organic arsenical compounds, Ehrlich's concept of " therapia sterilisans magna " dominated the field, but Ehrlich himself foresaw the problem of drug-fastness in chemotherapy and, recognizing inadequate dosage as its most frequent cause, emphasized the dangers of under-treatment at several international conferences From 1920 to 1940 many reports on treatment-resistant syphilis were published by German and French workers Beerman (1936) lists 430 references Most of these reports discuss resistance to arsenical therapy and some to bismuth

Silberstein (1924) classified treatment-resistance in primary and secondary syphilis as follows

(1) Primary Resistance—resistant from the start
(2) Primary-Secondary Resistance—after initial involution a resistant recurrence develops
(3) Secondary Resistance—arsenical treatment heals the lesions, but after a latent period a resistant recurrence appears

Gougerot (1923, 1931) and Nicolas, Lacassagne, and Froment (1930), cited by Beerman (1936), give a more elaborate classification based on the degree of resistance

(1) Attenuated resistance
(2) Treatment recurrence
(3) True treatment-resistance
  (*a*) primary,
  (*b*) secondary
(4) Treatment activation or stimulation

The increase of treatment-resistant syphilis in the pre-penicillin era was reported almost exclusively from France and Germany, the criteria of resistance being

(*a*) persistence of lesions,
(*b*) persistently positive blood serology tests,
(*c*) persistence of *Treponema pallidum* in spite of adequate treatment, the last being the most reliable

The most common clinical types of treatment-resistant syphilis occur in early infections and are usually cutaneous The lesions may be typical or atypical They are stated to have a predilection for the face, nose, neck, penis, and upper extremities, and are usually atypical at the time of their appearance Precocious tertiarism is present in many of these cases and chancriform recurrences are frequently reported The blood serological reaction tends to be negative more frequently in treatment-resistant early syphilis The host seems to play the key role in treatment-resistance through inability to metabolize the drugs used, failure of defensive powers, endocrine dysfunction, hepatic insufficiency, and so on Clinical evidence supported by *in vitro* laboratory studies suggests that small subcurative doses of a treponemicidal drug and inadequate treatment are more likely to cause treatment-resistance than the quality or brand of the drug used Sometimes resistance may be overcome by changing to another drug

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for a period of 4 months and subsequently responded to penicillin and fever therapy

Hahn (1947) reported a case of late gummatous syphilis of the penis which failed to heal after 4 8 mega units penicillin but which responded promptly to therapy with mapharsen and bismuth Reynolds (1948), reporting treatment failures with penicillin in late syphilis, cautioned against the *a priori* supposition that penicillin alone would be as efficacious in late as in early syphilis He classified penicillin failure in late syphilis as follows

(1) drug resistance with failure of overt manifestations to heal,

(2) clinical progression despite therapy,

(3) recurrence of lesions after an initially favourable response,

(4) subsequent development of new lesions elsewhere in the body

In laboratory studies of susceptible bacteria it has been demonstrated that penicillin has been found to be active *in vitro* against rapidly multiplying organisms in the phase of active growth, but inactive against the same organism in the resting phase Reynolds (1948) postulates a comparable activity *in vivo* of penicillin against *Treponema pallidum* and tries to explain the failure of penicillin in late syphilis when the organisms are supposed to be few in number and not rapidly multiplying as in acute early syphilis

Most of the reported failures belong to the first two or three years of penicillin therapy, when the antibiotic was impure and dosage schedules were still in the trial stage Since the isolation of pure crystalline penicillin G and the introduction of repository penicillin we find fewer reports of failure or of resistance to penicillin therapy in late syphilis Furthermore, in late syphilis resulting in destruction or degeneration of tissues, penicillin cannot be expected to achieve a miracle of quick healing or to repair the damage While penicillin destroys the treponemata, the reparative powers of the body must produce healing Again, the pathology of late syphilis, with its vascular occlusion and fibrosis, prevents the circulating penicillin from gaining access to the active foci of infection, hence its action is delayed, and a larger total dosage over a longer period of time may be necessary to cure or arrest the disease process The concept of true resistance, either primary or secondary, cannot be strictly applied to the lesions of late syphilis, on account of its inherent pathology and immunology Reynolds was right in suggesting that adjuvant measures, such as the concurrent use of fever therapy, may be necessary to achieve rapid healing and avoid relapse The iodides, which promote the absorption of granulomatous and fibrous tissues, have recently gone out of use, but they may still have some value in late syphilis

Case Report

The authors are not aware of a case similar to the following having been described in the literature This patient has been under observation for 11 years, from August, 1943, to May, 1954, and has been given various courses of treatment with every available form of therapy punctuated by periods of default In April, 1949, he appeared to be clinically cured, but as he was still strongly sero-positive further malarial therapy was suggested, however, he could not be persuaded to undergo the ordeal of fever, which he had already tried in 1946, and was discharged

After 5 years of well being with no clinical recurrence, he again presented himself on May 15, 1954, with a fresh ulceration of the orbit of one month s duration At the time of writing he is still under treatment with PAM and bismuth and the ulceration is healing

The progress of this patient for over 10 years is set out in the Table This prolonged resistance to treatment of syphilitic infection is unique in that it cannot be classified by any of the criteria outlined by various European investigators The initial inadequate therapy of early syphilis is the basis of the subsequent evolution of the disease After mapharsen, bismuth, and fever had failed the resistance to therapy was broken in 1947 by the introduction of penicillin but two fresh successive penile gummata appeared in 1948, the first of which responded promptly to mapharsen and bismuth and the second to penicillin Then, after 5 years freedom from symptoms, the disease broke out again When he was examined on February 14, 1955, the ulceration at the orbital margin had healed and there was no evidence of fresh lesions He was still VDRL positive but showed decline from 128 to 32

TABLE

PROGRESS OF TREATMENT RESISTANT SYPHILIS

Episode	Period of Observation		Clinical Findings	Laboratory Findings	Treatment		Remarks
	Year	Date			No of Injections	Drug	
I	1943	Aug 19–30	Florid secondary syphilis with indurated penile lesions	Dark field positive for *T pallidum* Kahn and W R strong positive	3	0 04 g mapharsen	Lesions healing
					3	0 2 g bismuth	

continued

TABLE—*continued*

Episode	Period of Observation: Year	Period of Observation: Date	Clinical Findings	Laboratory Findings	Treatment: No of Injections	Treatment: Drug	Remarks
			FIRST DEFAULT				
II	1943 to 1944	Dec 23 to Feb 14	Penile lesions healed Cutaneous papular eruptions completely disappeared Multiple discrete destructive crusted ulcers on face trunk and limbs Loss of weight	Dark field positive Kahn and W R strong positive	6 6	mapharsen bismuth	Malignant precocious tertiarism
			SECOND DEFAULT				
III	1944	Mar 3 to Aug 30	Ulcers not healed Lesions on left knee showing evidence of extension	—	18 18	mapharsen bismuth	Lesions on trunk and face slowly healing but on left knee refractory and spreading
			THIRD DEFAULT				
IV	1944 to 1945	Dec 4 to Mar 28	Nodulo cutaneous ulcerations on left knee and leg unhealed (Fig 1)	Kahn and W R strong positive	13 13	mapharsen bismuth	No evidence of healing
			FOURTH DEFAULT				
V	1945	April 28 to July 23	Lesions on left knee and leg unhealed and slowly spreading Ulcers on trunk and face completely healed	—	10 10	mapharsen bismuth	No evidence of healing
	1945 to 1946	Aug 4 to Feb 6	Lesions on left knee and leg showed a little healing but were spreading peripherally Painful tender swelling on dorsum of right hand Commencing gummatous osteomyelitis of metacarpal bone of middle finger (Fig 2)	—	13 11	mapharsen bismuth	Cerebrospinal fluid no abnormality
	1946	Feb 22 to Mar 5	—	—	Six sessions of fever with T A B vaccine		—
	1946	Mar 16 to Aug 24	—	—	25 14	mapharsen bismuth	On August 24 1946 lesions on left knee and leg completely healed Swelling of dorsum of right hand persisting
			FIFTH DEFAULT				
VI	1947	Nov 7 to 28	Multiple crusted sinus ulcers on dorsum of right hand (Fig 3) Extensive necrotic ulceration with polycyclic border on lateral aspect of right upper arm (Fig 3) Nodulo cutaneous ulceration on left side of nape of neck Ulceration of right nostril	Kahn and W R strong positive	3 8 mega units aqueous penicillin Pot iodide by mouth Course of liver extract injections		All lesions dramatically healed by Nov 28 1947 Shortening of middle finger of right hand with complete destruction and disappearance of distal half of metacarpal bone (Fig 4)
			DISCHARGED				
VII	1948	Feb 27 to July 17	Gummatous ulcer on dorsal aspect of prepuce	Dark field negative Kahn and W R strong positive	10 10	mapharsen bismuth	Ulcer healed
			DISCHARGED				
VIII	1948	Dec 22	Gummatous destructive ulceration on penoscrotal junction extending to under surface of penis (Fig 5)	Dark field negative Kahn and W R strong positive	6 mega units aqueous penicillin		—
	1948 1949	Dec 26 to Jan 11	—	—	—		Ulceration rapidly healed
	1949	April 27	No fresh recurrence and clinically free	Kahn and W R strong positive	Further fever therapy refused		Cerebrospinal fluid negative Cardiovascular system normal
			FIVE YEARS SYMPTOM FREE				
IX	1954	May 15	Nodulo cutaneous crusted ulceration on lateral aspects of left orbital margin (Fig 6) Scars of past ulceration	VDRL positive Titre 128 dilutions	PAM 2 ml daily for 25 days Bismuth 1 ml weekly		Ulcer healing Patient still under observation
X	1955	Feb 14	No ulceration or fresh lesions	VDRL positive Titre 32 dilutions	—		Cerebrospinal fluid no abnormality

FIG 1.—Scar of resistant nodulo cutaneous ulceration on left knee and leg (1944–46) See Table part IV

FIG 2.—Scar of healed gummatous ulceration of dorsum of hand and right upper arm (1945–47) Note shortening of middle finger See Table part V

FIG 3.—Gummatous ulcerations of dorsum of right hand and upper arm (1947) See Table part VI

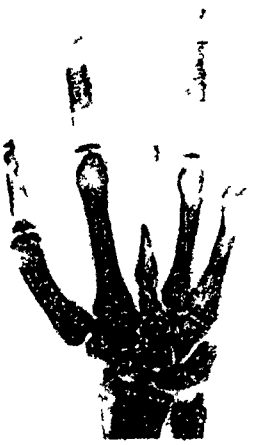

FIG 4.—Radiograph showing destruction and shortening of metacarpal bone of right middle finger (1947) See Table part VI

FIG 5.—Hypopigmented scar of gummatous ulceration on under surface of penis (1948) See Table part VIII

FIG 6.—Nodulo-cutaneous ulceration of left orbital margin (1954) See Table part IX

Comment

The prolonged resistance of the infection to mapharsen, bismuth, and fever over a period of 3 years, after penicillin therapy, the subsequent response to penicillin, the three further recurrences, and the satisfactory healing of these later lesions with mapharsen, bismuth, and penicillin seem to suggest that not the drugs but the tissues of the host are responsible for treatment-resistance and recurrence The role of the parasite in treatment-resistance is difficult to evaluate unless the chemo-resistance can be transferred to experimental animals

Summary

A case of unusually prolonged, treatment-resistant syphilis with recurrences is reported Inadequate treatment of the original infection seems to have induced an inveterate allergic sensitivity in the tissues of the host After 3 years of resistance to prolonged concurrent therapy with mapharsen and bismuth, the lesions responded dramatically to the first course of penicillin, but new manifestations appeared at varying intervals from 4 months to 5 years after the first course of penicillin These new lesions have healed both with the arseno-bismuth combination and with penicillin It is not possible to foresee whether the patient will be free from further trouble The treatment-resistant lesions were cutaneous and skeletal

The authors wish to express their thanks to the staff of the Barnard Institute of Radiology for the clinical photographs and radiograph and to Sri K Parthasarathy of the Venereal Diseases Department, Government General Hospital, Madras, for his help rendered in bringing in the patient periodically for examination.

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YAWS IN MANCHESTER *

BY

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Yaws is found in underdeveloped areas lying between the Tropics of Cancer and Capricorn It is a contagious treponematosis usually affecting non-white communities living in primitive and impoverished circumstances in areas of heavy rainfall, lush vegetation, and high humidity Infection is probably spread by direct contact in childhood and is facilitated by abrasions of the sweat-sodden skin unprotected by the almost complete absence of clothing The primary lesion, when noted, is commonly found on the feet, legs, or buttocks, and is followed by the secondary stage which is characterized by *multiple papillomata, often yellow-crusted* and fly-covered and always highly infectious Bone lesions—periostitis and osteitis—occur as late secondary and tertiary manifestations causing pain, and often inability to work Destructive skin lesions, *juxta-articular nodes, ganglion, and bursitis* are typical tertiary lesions Hyperkeratoses of the soles and palms may be infectious and are often painful, preventing the sufferer from working, a feature of great economic and epidemiological importance in areas where the incidence is high In the absence of adequate treatment, which for various reasons has seldom been possible in endemic areas in the past, relapses are common and much morbidity and impoverishment result Yaws is rarely a direct cause of death and late involvement of the cardio-vascular and central nervous systems is generally thought not to occur The behaviour of the standard serological tests is essentially similar in yaws and syphilis Bony deformity, commonly of the tibiae, and 'cigarette-paper" scars on the lower extremities are suggestive evidence of previous infection in individuals who have grown up in endemic yaws areas The infection and its non-venereal method of spread are widely recognized by the affected communities, some believe that childhood yaws prevents venereal syphilis later in life and may therefore deliberately encourage the infection of the children and refuse treatment until after the secondary stage has passed For those who have experience of both venereal syphilis in civilized communities and of yaws "at the end of the road", the "unitarian" hypothesis of Hudson (1946) has much to commend it, it seems likely that in yaws we see the original non-venereal treponematosis of primitive man, which, modified by civilization and environment, can now only spread by the intimate contact of sexual intercourse in adults and thus manifest itself as venereal syphilis

In tropical countries the areas in which yaws is endemic are usually well demarcated and in such parts venereal syphilis is reported to be rare The differentiation between yaws and syphilis is thus assisted by and sometimes rests on geographical location This factor is only of value as long as the population remains static, it ceases to be of assistance when individuals leave their native homes to journey long distances particularly overseas In recent years there has been a considerable immigration from West Africa and the West Indies to England, and Manchester, like other major centres of industry, has received an influx of workers from places in which yaws is, or was until recently, endemic These men are particularly exposed to venereal disease after their arrival in England as they are usually without friends in a strange land and seek sexual outlet amongst the prostitutes and the most promiscuous "amateurs" They provide a considerable proportion of the cases of gonorrhoea and non-gonococcal urethritis currently treated in the V D departments of Manchester and many present themselves time and again with fresh infections Although infectious venereal syphilis is almost unknown in the Manchester area at present, serological tests for syphilis are not infrequently found to be positive in such coloured patients, in interpreting the significance of these positive tests,

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the possibility of their having arisen as a result of yaws in childhood or adolescence has been considered This point is not solely of academic interest, as a firm diagnosis of old yaws will modify the amount of treatment thought necessary and the ultimate prognosis for the individual, and will attenuate anxiety if the patient, as frequently happens, ceases treatment prematurely Differentiation is also important in the relatively few female coloured patients who have been found in the course of routine antenatal testing Furthermore, these patients from the Colonies are tending artificially to maintain the figures for late syphilis in the annual returns sent to the Ministry of Health, and further experience may point to the desirability of modifying the form of the return to include late yaws as a separate item

Experience in Manchester

Impressed by the medico-social problem provided in Manchester by the presence of the immigrants from West Africa and the West Indies, and having had my interest in yaws stimulated by study of the condition in Ceylon and Thailand, I have looked into the current records of the coloured patients attending St Luke's Clinic and the V D Department of the Royal Infirmary, Manchester, in whom serological tests for syphilis had given a confirmed positive result The nationality of these 48 patients (45 males and 3 females) was

West Indian	12
West African	30
Ceylonese	1
Indian	1
No data	4
Total	48

Their ages ranged from 21 to 45 years (average 28 2), eighteen were aged between 20–25 years, fourteen 26–30 years, and sixteen were over 30 years old

Serological testing had been undertaken for the following reasons

Routine in gonorrhoea or urethritis	34
Herpes genitalis	1
Epididymitis	1
Rash (secondary syphilis)	1
Investigation by medical unit	4
Patient requested blood test	3
Routine antenatal test	3
No data	1
Total	48

Old periostitis of the tibia with residual thickening and irregularity about the middle of the tibial shaft was noted in thirteen cases Suggestive scarring was present on the legs alone in eleven, legs and abdomen in one, and legs and trunk in one Tibial periostitis and scarring were found together in nine patients, periostitis without scars in four, and scarring alone in two

The standard serological tests gave the following results

Wassermann Reaction	
High titre (1 8 or greater dilution)	17
Low titre (less than 1 8 dilution)	26
Negative	5
Kahn Test	
Positive	47
Doubtful	1
Negative	0

Fourteen patients (eleven males and three females) knew that they had had yaws, and six of these had had a few injections for it Two patients had been infected at 7 years, one at 11 years, and the other ten "as a child" Three gave a history of yaws in parents or siblings Ten denied having had yaws and in 24 no information was available

The nationality of the fourteen patients with a definite history of yaws was

	Male	Female
West Indian	0	2
West African	8	0
Ceylonese	0	1
No data	3	0

Only four of these presented tibial changes on clinical examination

The history and clinical findings suggest that the positive serological tests were due to yaws in 26 cases (23 males, three females), their nationality was as follows

	Male	Female
West Indian	5	2
West African	15	—
Ceylonese	—	1
No data	3	—
Total	23	3

The eldest was aged 40 and the youngest 22 (average 28 5) Ten were aged 20 to 25 years, seven 26 to 30 years, and nine were over 30 years of age

The results of serological tests in these 26 patients were

Wasserman Reaction	
High titre	10
Low titre	14
Negative	2
Kahn Test	
Positive	26
Doubtful	0
Negative	0

Discussion

The differentiation between late yaws and syphilis is difficult and sometimes impossible in persons

born and bred in yaws areas who have subsequently lived a promiscuous sexual life in more highly civilized communities In consequence the diagnosis reached in some of the cases analysed above is by no means dogmatic It is confidently felt, however, that yaws is the true diagnosis in at least half of the 48 patients studied One patient had unequivocal evidence of secondary syphilis, one had herpes genitalis (dark-field negative), but the remaining 46 had neither genital ulceration nor scars No case presented a clinical cardiovascular lesion, and except for tibial changes, none showed any stigmata of congenital syphilis

The 26 patients thought to be examples of late yaws included two patients in whom knee and ankle reflexes were absent without other evidence of tabes dorsalis One was a Nigerian, aged 36 years, with well-marked tibial changes, and the second was a Jamaican, aged 40, with typical tibial changes and scarring of the legs who stated that a sibling had had yaws Neither had been treated in childhood and superinfection or neurological damage from yaws are interesting speculations A third in this group was a Jamaican, aged 32, who had leprosy, and, on investigation for headache, was found to have a positive Wassermann reaction in both blood and cerebrospinal fluid The treponemal immobilization test was also positive, and there were suggestive scars over the trunk and legs and a history of yaws, untreated, in childhood

It will be noted that in many of the 48 cases the titre of the positive tests was not high and this observation at first seems to favour yaws infection of 15 to 20 years' duration rather than early latent acquired syphilis However, in view of the age and composition of the series, these patients were old enough to have acquired syphilis some 10 or more years before our investigation took place

Yaws normally affects both sexes almost equally with a slight predominance in boys The sex distribution in the present series is quite artificial, as the sample is drawn from immigrants amongst whom males strongly predominate

The impression was gained that more of the West Indians than the West Africans were born and grew up in towns rather than rural villages, this would favour a higher incidence of yaws in the immigrants from West Africa

It is felt that, in the interpretation of positive serological findings, the possibility of yaws should be considered in all coloured patients seen in England who have emigrated from countries in which yaws is known to be endemic It may also rarely have to be considered in white patients who have spent some of their childhood in such countries The latter possibility is illustrated by a case seen personally in Suffolk in 1953 The patient, born in October, 1945, was taken to East Africa some 5 months later He suffered various illnesses including malaria, and when 1 year old developed a lesion on the dorsum of the right foot which was excised under general anaesthesia He returned to England in March, 1948, and remained in England until July, 1952, when he sailed to West Africa to spend the summer vacation with his parents On board ship on his way *to* West Africa he developed bilateral tibial periostitis and an eruption on the trunk which responded dramatically to one injection of penicillin On his return to England with his parents in September, 1952, a radiograph of the tibial periostitis, which was still painful, was reported as "syphilitic periostitis" Radiography also showed similar involvement of the bones of the forearms and thighs The Wassermann reaction and Kahn test were positive but both parents and his elder brother were completely negative on clinical and serological examination The bone pain settled with penicillin treatment and when I first saw him in August, 1953, aged almost 8 years there were no stigmata of congenital syphilis other than periosteal thickening of both tibiae The permanent incisor teeth were normal A scar was present over the dorsum of the right foot where the lesion had occurred in 1946 The patient has had further treatment with penicillin, and is clinically well, but the serological tests remain positive although the cerebrospinal fluid is normal There seems no doubt that this is a genuine example of yaws in a white child

Summary

The influx of immigrants from West Africa and the West Indies to Manchester has been reflected in the increased number of coloured male patients seen in the V D clinics A considerable number of these men have positive serological tests for syphilis and there is evidence in some cases that the serological results arise from childhood infection with yaws in their native land A case of a white child is reported in which yaws was acquired as a toddler in East Africa It is suggested that in the interpretation of positive serological tests in coloured immigrants yaws should be considered in differential diagnosis

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EFFECT OF ROOM TEMPERATURE ON SEROLOGIC TESTS FOR SYPHILIS*

BY

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The maintenance of uniform levels of performance in serological tests for syphilis is dependent upon many factors Three of the most important are

(1) strict adherence to an accepted, published technique,
(2) the use of standardized reagents,
(3) the temperature at which the tests are performed

The effects of temperature on the results obtained in the older serological tests for syphilis employing lipoidal antigens is well known In fact, the differences in test results obtained when certain tests were performed at different temperatures served not only as the basis for attempted differentiation of syphilitic from so-called biologic false positive reactions (Kahn, 1940), but also for determining the relative specificity of different lots of lipoidal antigens (Kline and Suessenguth, 1946)

Other workers have shown that test sensitivity is affected not only by the temperature at which the antigen-saline emulsions are prepared (Cannefax and others, 1953) but also by the temperature of the glassware and reagents (Fugazzotto, 1953) Exposure of blood or serum samples to temperatures above those employed for refrigeration increases the rate of haemolysis on the one hand and depresses the serological titre on the other, in proportion to the duration of exposure and the elevation of temperature Most of the widely used serological tests for syphilis, with the exception of those performed at 4 to 6° C or 37° C, are carried out at so-called "room temperature", but this term becomes meaningless when the wide seasonal variations in laboratory temperatures which occur nationally and internationally are considered

In order to show the effect of these temperature variations on serological tests for syphilis, other than those employing refrigerator temperature or incubation at 37° C, and to determine optimal temperature limits for performance of these tests, comparative tests were performed using six selected techniques at temperatures ranging from 15 to 40° C (60 to 100° F) The purpose of this report is to present the results obtained when both whole serum and serum diluted with saline were tested with the Kahn test employing lipoidal antigen and the Kline, Mazzini, Rein-Bossak, and VDRL slide and tube tests using cardiolipin-lecithin antigens, between these temperature limits

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Method

Sera —Individual *pools* of serum of varying degrees of reactivity were collected, Seitz-filtered, separated into aliquots, and stored without preservative at −20° C until tested One set of aliquots was removed from the deep-freeze cabinet on each testing day, thawed, mixed thoroughly, and heated at 56° C for 30 min before testing To reduce technical differences to a minimum, testing at any given temperature was repeated on three separate testing days with aliquots of the same group of sera, although several groups of different sera were employed during the study Dilutions of dehydrated serum in saline also were included each time tests were performed

Performance of Tests —All the techniques used were performed exactly as described in the "Manual of Serologic Tests for Syphilis, 1949" Glassware, reagents, and equipment were allowed to reach the temperature at which the tests were being investigated before antigen emulsions were prepared and the tests performed

Antigens for the tests were prepared and standardized at the Venereal Disease Research Laboratory, with the exception of one lot of Kahn antigen, obtained from the University Hospital, Ann Arbor, Mich, and one lot of Kline antigen, which was purchased from the LaMotte Chemical Company, Baltimore, Md

Results

The results obtained with the tests performed in this study are listed in Tables I, II, and III Table I shows the findings obtained in initial testing at two extremes of temperature, 15 and 40° C, with 25° C included as an average representative room temperature Table II lists test results obtained within the narrower temperature limits of 21, 27, and 32° C Table III gives comparative results obtained at 23 and 29° C

Discussion

Slide Flocculation Tests—Results obtained with four slide flocculation tests, employing cardiolipin-lecithin antigens at various temperatures, are listed in Tables I, II, and III As shown in Table I, all four tests showed marked differences in reactivity when performed at 15 and 40° C Out of a total of sixty specimens tested, only four 3+ or 4+ reactions were obtained with the Kline test, none with the Mazzini, and six with the Rein-Bossak test, when tests were performed at 15° C By contrast, maximal (4+) reactions were obtained on all sixty specimens with each of the three tests when the room temperature was raised to 40° C Only two reactive results were obtained with the VDRL slide test at 15° C, 25 of the remaining test results were weakly reactive and 33 were non-reactive As the room temperature was increased to 25° C, non-reactive findings were reduced to six and reactive findings increased from two to 28 At 40° C, no non-reactive or weakly reactive results were obtained

Quantitative testing was likewise affected by temperature extremes End-point titres of some sera with the Kline test increased from less than 20 to 40 dils (Harris, 1947), with the Mazzini test from less than 20 to 80 dils, and with the Rein-Bossak from 40 to 160 dils Quantitative tests performed with the VDRL showed increases of at least a two-fold dilution when the room temperature was increased from 15 to 25° C

In order to establish temperature limits within which tests were minimally affected by room temperature, additional testing was performed within narrower temperature limits of 21 to 32° C (Table II) A slight increase in reactivity was noted in the results obtained with the Kline and Rein-Bossak tests when the operating temperature was increased from 27 to 32° C, and all four slide

TABLE I

COMPARATIVE RESULTS OBTAINED IN TESTS FOR SYPHILIS PERFORMED AT 15 25 AND 40 C

Test		Kahn Standard*			Kline Standard			Mazzini			Rein Bossak			VDRL Slide			VDRL Tube		
Temperature		15°C	25°C	40°C	15 C	25 C	40 C	15°C	25°C	40°C	15°C	25 C	40 C	15°C	25°C	40°C	15°C	25°C	40°C
Results	4+	24	24	1	0	19	60	0	38	60	0	22	60	—	—	—	—	—	—
	3+	18	22	8	4	9	0	0	6	0	6	10	0	—	—	—	—	—	—
	2+	16	14	5	18	16	0	0	12	0	10	13	0	—	—	—	—	—	—
	1+	2	0	7	8	14	0	0	4	0	14	15	0	—	—	—	—	—	—
	±	0	0	5	21	2	0	0	0	0	13	0	0	—	—	—	—	—	—
	Non reactive	0	0	34	9	0	0	60	0	0	17	0	0	33	6	0	0	0	2
	Weakly reactive	—	—	—	—	—	—	—	—	—	—	—	—	25	26	0	—	—	—
	Reactive	—	—	—	—	—	—	—	—	—	—	—	—	2	28	60	60	60	58
Totals		60	60	60	60	60	60	60	60	60	60	60	60	60	60	60	60	60	60
Quantitative Tests (dils)	Non reactive at 1 20	0	0	6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	<20	0	0	0	2	0	0	6	0	0	0	0	0	0	0	0	0	0	0
	20	6	6	0	2	4	2	0	0	0	0	0	0	4	0	0	0	0	0
	40	0	0	0	2	2	4	0	6	0	6	2	0	2	6	5	0	0	0
	80	0	0	0	0	0	0	0	0	6	0	4	4	0	0	1	1	0	0
	160	0	0	0	0	0	0	0	0	0	0	0	2	0	0	0	5	4	5
	320	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	1
Totals		6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6

*Lot 178 furnished by University Hospital Ann Arbor Mich

TABLE II

COMPARATIVE RESULTS OBTAINED IN TESTS FOR SYPHILIS PERFORMED AT 21 27 AND 32° C

Test		Kahn Standard*			Kline Standard			Mazzini			Rein Bossak			VDRL Slide			VDRL Tube		
Temperature		21°C	27°C	32°C	21°C	27°C	32°C	21°C	27°C	32°C	21°C	27°C	32°C	21°C	27°C	32°C	21°C	27°C	32°C
Results	4+	10	12	8	0	8	12	0	14	1[illegible]	6	14	19	—	—	—	—	—	—
	3+	15	18	10	7	10	6	6	4	3	[illegible]	7	4	—	—	—	—	—	—
	2+	15	11	15	10	4	4	8	4	5	7	3	2	—	—	—	—	—	—
	1+	6	7	13	5	3	3	7	3	3	3	0	1	—	—	—	—	—	—
	±	1	0	1	3	2	2	0	0	0	1	2	1	—	—	—	—	—	—
	Non reactive	13	12	13	5	3	3	9	5	4	5	4	3	19	[illegible]	9	6	5	6
	Weakly reactive	—	—	—	—	—	—	—	—	—	—	—	—	6	6	[illegible]	0	0	0
	Reactive	—	—	—	—	—	—	—	—	—	—	—	—	5	16	13	24	25	24
Totals		60	60	60	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30
Quantitative Tests (dils)	10	6	6	6	3	2	1	3	2	2	0	0	0	0	0	0	0	0	0
	20	0	0	0	0	1	2	0	1	1	3	2	0	3	3	3	0	0	1
	40	0	0	0	0	0	0	0	0	0	0	1	3	0	0	0	3	3	2
Totals		6	6	6	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3

*Antigen prepared and standardized at the Venereal Disease Research Laboratory

TABLE III

COMPARATIVE RESULTS OBTAINED IN TESTS FOR SYPHILIS PERFORMED AT 23 AND 29° C

Test		Kahn Standard		Kline Standard		Mazzini C-L		Rein Bossak		VDRL Slide		VDRL Tube	
Temperature		23° C	29° C	23° C	29° C	23° C	29° C	23° C	29° C	23° C	29° C	23° C	29° C
Results	4+	13	13	8	25	22	23	24	23	—	—	—	—
	3+	4	5	17	2	4	4	3	1	—	—	—	—
	2+	5	2	2	0	1	0	0	3	—	—	—	—
	1+	4	4	0	0	0	0	0	0	—	—	—	—
	±	0	1	0	0	0	0	0	0	—	—	—	—
	Non reactive	4	5	3	3	3	3	3	3	[illegible]	[illegible]	[illegible]	[illegible]
	Weakly reactive	—	—	—	—	—	—	—	—	[illegible]	2	0	0
	Reactive	—	—	—	—	—	—	—	—	26	[illegible]	27	27
Totals		30	30	30	30	30	30	30	3[illegible]	[illegible]	[illegible]	30	3[illegible]
Quantitative Tests (dils)	20	0	1	0	0	0	0	0	[illegible]	[illegible]	[illegible]	0	[illegible]
	40	3	2	3	3	1	0	0	[illegible]	[illegible]	[illegible]	0	[illegible]
	80	0	0	0	0	2	3	[illegible]	[illegible]	[illegible]	[illegible]	0	[illegible]
	160	0	0	0	0	0	0	[illegible]	[illegible]	[illegible]	[illegible]	2	[illegible]
	320	0	0	0	0	0	0	0	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Totals		3	3	3	3	3	3	3	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

flocculation tests were definitely less reactive when the room temperature was lowered from 27 to 21° C

Since it was desirable that optimal operating temperatures be established for as many of the serological tests as possible, the lower temperature limit was raised to 23° C and the upper limit lowered from 32 [illegible] testing was accomp[illegible] limits (Table III) [illegible] observed in the re[illegible] four techniques, [illegible] tests were perform[illegible] indicated, and it [illegible]

effect of temperature variants on the four slide flocculation tests employed in this study can be reduced to a minimum if testing is carried out at room temperatures between 23 and 29° C

VDRL Tube Test—As indicated in all three Tables, no significant variation in reactivity was noted in either qualitative or quantitative results when tests were performed at any of the listed temperatures ranging from 15 to 40° C

Kahn Test—*The test results listed in Table I were obtained with a lot of Kahn Standard antigen* obtained from the University Hospital, Ann Arbor, Mich Little difference in reactivity was noted when the Standard Kahn test was performed at 15 or 25° C, although non-reactive results were quite turbid and difficult to read A marked drop in reactivity was noted, however, at 40° C

Whereas no non-reactive results were obtained in tests on individual sera at 15 and 25° C, 34 of the same sera dropped to negativity when tested at 40° C Similar results were observed in quantitative testing Six separate testings of serum diluted in saline produced identical end-point titres of 20 dils when tests were performed at either 15 or 25° C In all six instances, however, completely non-reactive results were obtained at the same dilution at 40° C The test results listed in Table II were obtained with a lot of Kahn Standard antigen prepared and standardized at the Venereal Disease Research Laboratory Little difference was noted in the results obtained in either qualitative or quantitative tests performed at temperatures between 21 and 32° C

Summary and Conclusions

The reactivity levels of all of the tests included in this study, with one exception, were affected in varying degrees by marked changes in the room temperature at which the testing was carried out

The Kline Standard, VDRL slide, Mazzini, and Rein-Bossak tests, employing cardiolipin-lecithin antigens, showed progressive decrease in reactivity in qualitative and quantitative testing at room temperatures below 23° C and became increasingly reactive at temperatures above 32° C

The VDRL tube test showed no significant variation in reactivity when performed at room temperatures between 15 and 40° C

Qualitative and quantitative Kahn test reactivity was significantly lowered when testing was performed at temperatures above 32° C No appreciable difference in reactivity was noted when tests were performed at room temperatures between 15 and 32° C

The effect of room temperature variants on serological test reactivity was reduced to a minimum when the tests employed in this study were performed between 23 and 29° C (73 to 84° F)

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VDRL SLIDE FLOCCULATION REACTION FOR SYPHILIS PERFORMED ON ACTIVE SERA*†

BY

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The discovery of cardiolipin (Pangborn, 1941a) as the active agent in antigens for sero-reactions for syphilis enabled the production of chemically defined antigens, composed of cardiolipin, purified lecithin (Pangborn, 1941b), and cholesterol

Among the many tube and slide flocculation reactions based on the use of cardiolipin antigens, the Venereal Disease Research Laboratory (VDRL) slide flocculation reaction for syphilis, as described in the *Manual of Serologic Tests for Syphilis* (1949), has gained a world-wide reputation because of its specificity, sensitivity, and simplicity

All the well established sero-reactions for syphilis except two—the Meinicke tube and slide flocculation reactions (Meinicke, 1917 , Meinicke and Holthaus, 1933 , Meinicke and Fischer, 1939 , Kvittingen, 1948 , Schmid and Velaudapillai, 1953) and the Citochol slide flocculation (Schmid and others, 1953) —depend on the use of inactivated sera Whether this inactivation is performed at 56° C for 30 min or at higher temperatures for a shorter time, there is always the need of special equipment, the risk of sera becoming unsuitable for the test, and the risk of loss of time

The postulation of chemically defined and hence uniform batches of antigens is not met by the antigens for the Meinicke and Citochol reactions on active sera, because the former (though Meinicke and Brauer (1953) reported on the use of cardiolipin in its composition) contains balsam of Tolu, which is not a chemically defined substance, instead of cholesterol, and the latter antigen belongs to the group of " crude " heart extract antigens

It seemed therefore worth while experimenting to develop a VDRL test modified for the use of active sera

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Methods

Stabilization of active sera, similar to that of heat inactivation, can be obtained by the use of hypertonic saline (Sachs, 1921 , Sachs and Georgi, 1921 , Georgi and Lebenstein, 1921) The influence of various saline concentrations, of various concentrations of cardiolipin, lecithin, and cholesterol, and of the presence or absence of formalin, which is known to act as an inhibitor (Dold, 1921), was carefully studied on 25,645 active sera in parallel with the original VDRL test using the same but inactivated sera In the same way the influence of different speeds of rotation (Klein and others, 1952), and of varying " ripening " times of the prepared new antigen emulsion was also investigated

From the knowledge thus gained on the interactions of these variables, we were able to specify the technical requirements of a new test

Technique

The general equipment for this reaction is the same as for the original VDRL test, except that capillary pipettes with rubber teats were used These capillary pipettes are cut at the 56 hole of *Stairet's* gauge, and deliver 0 025 ml serum or saline per drop The amount of antigen emulsion delivered is 0 021 ml per drop

Buffered saline solutions of 1, 4, and 10 per cent sodium chloride are required They are best made by preparing 1 and 10 per cent solutions separately The second (10 per cent) is diluted 1 2 5 with distilled water to yield the required lower concentration of 4 per cent sodium chloride This dilution should be freshly prepared every working day The formula of these buffered saline solutions is the same as for the original VDRL test, except that 100 g sodium chloride per litre is used to prepare the 10 per cent solution

Sera —These are separated from the clot, and, if necessary, freed from red corpuscles by centrifuging, and are then ready for use

Antigen —Commercially available VDRL antigen

Preparation of Antigen Emulsion —Pipette 0 75 ml 1 per cent buffered saline to the bottom of a 40 ml bottle

Add 1 05 ml antigen directly into the saline while rotating the bottle gently but continuously on a flat surface Approximately 10 sec is allotted for this procedure Continue rotating for 20 more seconds *Avoid splashing saline on the antigen pipette*

Add 8 2 ml 1 per cent buffered saline, close the bottle, and mix well by vigorous shaking for 30 sec

Add 5 0 ml 10 per cent buffered saline, close the bottle, and mix well by vigorous shaking for 30 sec

The antigen emulsion is left for 15 min at room temperature for ripening, and is then ready for use This amount is sufficient for about 350 sera It is tested on known positive, doubtful, and negative sera If more sera are to be examined, twice that amount may be prepared in one procedure If still larger quantities of antigen emulsion are required, it is advisable to prepare it in separate mixtures and to pool these preparations in a suitable bottle

Experiments were carried out to evaluate the storage quality of the antigen emulsion by keeping it in the refrigerator (4° C) for 11 days with comparative daily tests on a total of 1,505 sera It was found that the antigen emulsion remains usable for 4 days, which we consider of economic advantage to smaller laboratories where less than 350 sera were examined per day It is important to resuspend the particles of the emulsion by gentle shaking when the bottle containing the antigen has been allowed to stand

It cannot be over-emphasized that all measurements for the preparation of the antigen emulsion are to be made with great accuracy To avoid measuring small fractions of a millilitre we thought it advisable to try an antigen specially prepared to suit the requirements of this new sero-reaction with simple measurements

With this antigen (*Istituto Sieroterapico Vaccinogeno Toscano "SCLAVO", Siena, Italy*), the preparation of the antigen emulsion follows the procedure of the original VDRL test except for the addition of 10 per cent saline, *i e*

0 4 ml 1 per cent buffered saline + 0 5 ml antigen + 4 1 ml 1 per cent buffered saline + 2 5 ml 10 per cent buffered saline

The requirements for timing, rotation, shaking, ripening, and preparation of larger batches, as described above, must also be observed This amount of antigen emulsion is sufficient for about 170 sera

Performance of the Test —All measurements of the test are made with the capillary pipettes described above Washing the pipettes three times in physiological saline and blowing them against a filterpad after each step permits the same pipette to be used throughout the test

One drop of the serum is distributed into each wax ring, then one drop of antigen is added and the slides are rotated at 120 r p m for 4 min with a rotating diameter of 2 in

Another drop of antigen and one drop of 4 per cent buffered saline are then added to each wax ring and the slides are rotated at the same speed for another 3 min Then the results are read by the naked eye or with the help of a hand lens (× 6)

In hot dry climates the use of a moist chamber may be necessary for the first rotation to avoid undue evaporation If no electric rotator is available, rotation can easily be carried out by hand on a flat surface

The results are recorded as negative (−) showing a homogenous opacity, doubtful (±) with a few and small flocculations, and positive (+) with more and larger aggregates, up to clarification with very large and scattered particles

Results

The results obtained with this new technique in 15,000 sera, are compared with the VDRL test on the same but inactivated sera (Table I)

TABLE I

Active Sera \ Inactivated Sera	−	±	+	Total	Percentage
−	13 163	83	50	13 296	88 64±0 26
±	88	88	101	277	1 85±0 11
+	36	64	1 327	1 427	9 51±0 24
Total	13 287	235	1 478	15 000	
Percentage	88 58±0 26	1 57±0 10	9 85±0 24		

None of the listed differences between these two tests is statistically significant, as they are all covered by less than a two-fold standard deviation

When the results of comparing the two tests are reported in percentages of agreement, it is evident that a large number of non-reactive sera contributes favourably towards a high percentage of agreement The evaluation of the percentage of agreement among reactive sera is therefore considered to be a more representative figure (Table II, opposite)

The agreement between these two reactions is very high, *i e* 98 29 and 86 01 per cent respectively The χ^2 test was applied to these figures and proved that

TABLE II

Number of Sero reactions					Per centage Agreement	Per centage Reactors	Percentage Agreement among Reactors
Inactive	—	—	R	R			
Active	—	R	—	R			
Total	13,163	124	133	1,580	98 29	12 25	86 01

the different numbers of reactive sera for each test are statistically not significant ($\chi^2 = 0\ 3375$)

Discussion

The above results show that our new test using active sera equals the VDRL test on inactivated sera

We have omitted a separate analysis of clinically diagnosed sera for two main reasons

(*i*) The sensitivity and specificity of the VDRL test is well established

(*ii*) Previous experience (Schmid and others, 1953) has shown that the number of clinically diagnosed sera is only about 15 per cent of the total sera investigated

This new modification of the VDRL test offers three definite advantages

(1) work with active sera,
(2) use of simple drop pipettes,
(3) ability to store the antigen emulsion for 4 days

The postulation of a chemically defined antigen is also met

Summary

A new modification of the VDRL slide flocculation reaction for the use of active sera is described

We wish to thank the *Istituto Sieroterapico Vaccinogeno Toscano "SCLAVO", Siena, Italy*, for putting at our disposal various batches of the modified new antigen along with their "Microgen" brand of VDRL antigen

Our thanks are also due to Messrs N E L Ponnuswamy and A L Dassanayake, for their assistance in performing the various tests in the laboratory

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COMPARISON OF THE IDE AND HARRIS (VDRL) SLIDE FLOCCULATION TESTS IN NIGERIA*

BY

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For over 10 years the Ide test has been in use in Nigeria as a simple slide flocculation test for syphilis and yaws in hospitals and clinics, and in the field, where the Kahn and Wassermann tests are impracticable It was thought desirable that the results obtained by the Ide test should be compared with those obtained by the newly introduced Harris (VDRL) slide flocculation test, and an estimate made of the relative values of the two tests for use in the field

The sera of 8,077 Nigerian subjects were therefore tested in parallel by the Ide, Harris, and Kahn tests The Kahn test was used as the basis on which the comparison should be made for two reasons

(*a*) It is the test which has been so far the most fully investigated as regards the comparison of clinical with serological findings

(*b*) It is the standard routine test in use in this laboratory

Material

Most of the 8,077 sera were received from the hospitals and clinics of the Lagos area The sera of yaws cases came from a Yaws Field Survey Unit, and the sera of lepers from a Leper Settlement, both in the Eastern Region of Nigeria The sources of the sera were as follows

Source	*No of Sera*
Antenatal Clinic (abnormal 451, normal 3 228)	3,679
Routine Medical Examination	420
Blood Donors	108
V D and Skin Clinic	395
Eye Clinic	595
E N T Clinic	220
Yaws Cases	204
Leprosy Cases	143
Other Sera	2,313
Total	8,077

(1) Ide Test

When Sobei Ide and Tamao Ide (1936) introduced their colour test for syphilis in Tokyo their antigen was an alcoholic extract of beef heart sensitized with cholesterol and containing gum benzoin, crystal violet, and azure II They recommended the use of whole blood diluted with 3 5 per cent saline and low-power magnification for the reading of the result In the Nyasaland Protectorate Annual Report for 1938, a modified Ide test was described in which it was claimed that the antigen had been made more sensitive by the replacement of beef heart by sheep heart

Smith, Elmes, and Smith (1945), in introducing the test to Nigeria, modified it as follows

(*i*) Serum was used instead of whole blood
(*ii*) Inactivation of the serum was suggested but not deemed a necessity
(*iii*) Readings were taken with the naked eye, with or without the use of a slit lamp

We have used the Smith, Elmes, and Smith method with the two following modifications

(*i*) The serum was always inactivated
(*ii*) The 2 5 per cent sodium chloride solution used to suspend the antigen was buffered to *p*H 6 1

By experiment it was discovered that the results of the tests were unreliable except when the *p*H of the saline solution lay between 5 9 and 6 3, the optimum being *p*H 6 1

Antigen—This is prepared as described in detail by Smith, Elmes, and Smith (1945), and must be stored in a cool, dark place The antigen-suspension is prepared by pipetting 1 5 ml of a 2 5 per cent solution of sodium chloride in distilled water (buffered to *p*H 6 1) and 0 5 ml antigen into separate vials The saline solution is poured on to the antigen, and, without pausing, the mixture is poured back and forth from vial to vial twelve times, without allowing the vials to drain during the process The thumb is then placed over the mouth of the mixing vial and the vial is briskly shaken for a few seconds This antigen suspension is ready for immediate use, and *must be used within 10 min* The suspension is first tested against known positive and negative sera, and it is discarded unless clear results are obtained in the control tests

Serum—Whole clotted blood is centrifuged and the clear serum removed by a pipette The serum is heated

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at 56° C for 30 min The test should be performed *within 4 hrs of inactivation of the serum*, serum to be tested more than 4 hrs after inactivation must be reheated at 56° C for a further 10 min Only clear serum should be used, a serum containing particulate matter should be re-centrifuged

Test—The optimal proportion of serum to antigen-suspension is 1 2 Mixing on a 3 in by 1 in microscope slide is performed with either glass pipettes with rubber teats (preferably standardized by the Starrett Gauge to No 56) or with platinum wire loops (6 mm) Separate pipettes (or loops) are used for serum and suspension The serum pipette is rinsed thoroughly in physiological saline after adding each serum (If a loop is used, it should be flamed and cooled after each serum) Two tests may conveniently be done on each slide

(*i*) Place 1 drop (or loopful) serum on slide

(*ii*) Add 2 drops (or loopfuls) antigen-suspension

(*iii*) Rotate slide for 3 min on a flat surface, through a circle of 2 in diameter, 120 times per min

(*iv*) Read immediately, holding slide over a dark background and viewing by reflected light with the naked eye (a slit lamp is a distinct advantage)

Interpretation

Reading	*Report*
No flocculation	Negative (−)
Small blue floccules	Positive (+)
Large blue floccules	Strongly Positive (++)

(2) Harris (VDRL) Test

We used the VDRL test as described by Harris and others (1946), with slight modifications

Antigen—VDRL cardiolipin antigen (Burroughs Wellcome and Co) was used It must be stored in a cool, dark place The antigen-suspension is prepared by pipetting 0 4 ml of a 1 per cent solution of sodium chloride in distilled water (buffered to *p*H 6) to the bottom of a 30 ml round, glass-stoppered bottle and adding 0 5 ml antigen from a 1-ml pipette (graduated to the tip), the bottle being continuously rotated on a flat surface The antigen is added drop by drop (taking approximately 6 sec), the last drop of antigen being blown from the pipette so that the pipette does not touch the surface of the saline solution The bottle is rotated for a further 10 sec and 4 1 ml physiological saline added The glass stopper having been replaced, the bottle is shaken vigorously for 10 sec The antigen-suspension is then ready for immediate use and *must be used within 24 hrs*, it should be stored in a cool, dark place The suspension is first tested against known positive and negative sera, and it is discarded unless clear results are obtained in the control tests

Serum—As for the Ide test (*vide supra*)

Test—The technique is the same as that of the Ide test, except that the optimal proportion of serum to antigen-suspension is 2 1

Interpretation—The reading and reporting of the result of the test is the same as in the Ide test (except that the floccules are white)

(3) Kahn Test

The Standard (three-tube) Kahn test was employed, "Wellcome" brand Kahn antigen being used throughout

Results

Of the total 8,077 sera, 1,134 were Kahn-positive Of these latter, 1,107 (97 6 per cent) gave a positive result with the Ide test, and 1,124 (99 1 per cent) gave a positive result with the Harris rest Of the 6,213 sera which were Kahn-negative, 6,071 (97 7 per cent) were negative to the Ide test, and 6,040 (97 2 per cent) to the Harris test

Seven hundred and thirty sera gave a Kahn-doubtful result, of these 505 (69 2 per cent) gave a positive result to the Ide test, and 565 (77 4 per cent) a positive result to the Harris test (Table I)

TABLE I

COMPARISON OF KAHN IDE AND HARRIS TESTS ON 8 077 SERA

Kahn Test			Ide Test			Harris Test		
Results	Number of Sera	Percentage of total Sera	Results	Number of Sera	Percentage in relation to Kahn Results	Results	Number of Sera	Percentage in relation to Kahn Results
Positive (++++)	289	14 0	Positive	289	97 6 agree	Positive	289	99 1 agree
			Negative	0		Negative	0	
Positive (+++)	434		Positive	431		Positive	434	
			Negative	3		Negative	0	
Positive (++)	411		Positive	387		Positive	401	
			Negative	24		Negative	10	
Doubtful (+ and ±)	730	9 0	Positive	505	69 2 positive	Positive	565	77 4 positive
			Negative	225		Negative	165	
Negative (−)	6 213	77 0	Positive	142	97 7 agree	Positive	173	97 2 agree
			Negative	6 071		Negative	6 040	
Total	8 077		Total	8 077		Total	8 077	

In Table II the results by the Ide and Harris tests are directly compared, and the χ^2 test is applied It will be seen that the difference favours the Harris test, but is not highly significant

TABLE II
COMPARISON OF IDE AND HARRIS TESTS ON 8 077 SERA

Test	Negative	Positive	Total
Ide	6 323	1 754	8,077
Harris	6 215	1 862	8 077
Total	12 538	3 616	16 154

χ = 4 1558
d f = 1
0 05 > P > 0 02

Discussion

These results show that there is very little to choose between the Ide and Harris tests, the balance being slightly in favour of the Harris test Both tests compare very favourably with the Standard Kahn test

In the course of the investigation, which occupied nearly a year, we decided that in both the Ide and Harris tests it was possible to make a differentiation in the positive results many were "strongly positive", the floccules developed rapidly and became large and very distinct We are not aware of the significance of these results , the clinical notes were not sufficient in number or detail to allow of a classification on clinical findings The differentiation, however, was marked enough to warrant a scrutiny of the positive results when divided into " Positive " and " Strongly Positive '

When this differentiation is taken into consideration there is a highly significant difference between the Ide and the Harris tests in favour of the latter (Table III)

TABLE III
COMPARISON OF IDE AND HARRIS TESTS ON 8 077 SERA DISTINGUISHING POSITIVE' AND STRONGLY POSITIVF

Test	Negative	Positive	Strongly Positive	Total
Ide	6 323	1 056	698	8 077
Harris	6 215	928	934	8 077
Total	12 538	1 984	1 632	16 154

χ = 43 3156
d f = 2
P < 0 001

Although, as has been mentioned, the clinical notes attached to the specimens of serum were on the whole insufficient, and the " follow-up " of cases was largely unsuccessful, it was thought worth while to make the attempt to divide the sera examined into two groups

(*a*) Sera from patients showing some evidence or suspicion of syphilis and/or yaws, present or past
(*b*) Sera from patients showing no such evidence

Vaughan (1947) states

> The evaluation of serological tests based on a comparison of results obtained by the examination of a series of unselected sera is rendered difficult by the absence of any practicable objective standards An attempt, however, was made to classify on clinical grounds all the sera examined as either syphilitic or non-syphilitic The results, being thus based on data open to subjective error, have no absolute value and cannot legitimately (except as an indication of broad trends) be compared with those of other workers

It is emphasized that our division of the sera into these two groups is based on scanty clinical notes (" data open to subjective error ") and was made only in the hope of finding an indication of broad trends

TABLE IV
COMPARISON OF IDE AND HARRIS TESTS ON 3,468 SERA FROM SUBJECTS SHOWING SOME EVIDENCE OR SUSPICION OF SYPHILIS OR YAWS

Test	Negative	Positive	Total
Ide	2 434	1 034	3 468
Harris	2 345	1 123	3 468
Total	4,779	2 157	6 936

χ = 5 3296
d f = 1
P = 0 02

Table IV shows the comparison of results given by the Ide and Harris tests on 3,468 sera, in which the clinical notes mentioned, or suggested, a history and/or signs and symptoms of syphilis and/or yaws The Harris test in this group was significantly more sensitive than the Ide test When the positive results in this group were divided into " Positive " and "Strongly Positive ', the greater sensitivity of the Harris test appears to be enhanced (Table V)

TABLE V
COMPARISON OF IDE AND HARRIS TESTS ON 3 468 SERA FROM SUBJECTS SHOWING SOME EVIDENCE OR SUSPICION OF SYPHILIS OR YAWS DISTINGUISHING BETWEEN POSITIVE AND STRONGLY POSITIVE

Test	Negative	Positive	Strongly Positive	Total
Ide	2 434	608	426	3 468
Harris	2 345	539	584	3 468
Total	4 779	1 147	1 010	6 936

χ = 30 5250
d f = 2
P << 0 001

When 3,993 sera from subjects showing no evidence or suspicion of syphilis or yaws were

examined there was no significant difference between the two tests (Table VI), but when the

TABLE VI

COMPARISON OF IDE AND HARRIS TESTS ON 3 993 SERA FROM SUBJECTS SHOWING NO EVIDENCE OR SUSPICION OF SYPHILIS OR YAWS

Test	Negative	Positive	Total
Ide	3 404	589	3 993
Harris	3,392	601	3,993
Total	6,796	1 190	7 986

χ = 0 1422
d f = 1
$0\,8 > P > 0\,7$

positive sera in this group were divided into "Positive" and "Strongly Positive" there was a highly significant difference between the tests, the Harris test being the more specific (Table VII)

TABLE VII

COMPARISON OF IDE AND HARRIS TESTS ON 3 993 SERA FROM SUBJECTS SHOWING NO EVIDENCE OR SUSPICION OF SYPHILIS OR YAWS DISTINGUISHING POSITIVE' AND STRONGLY POSITIVE

Test	Negative	Positive	Strongly Positive	Total
Ide	3 404	376	213	3 993
Harris	3 392	327	274	3 993
Total	6 796	703	487	7 986

χ = 11 0772
d f = 2
$0\,01 > P > 0\,001$

One reason for differentiating between "Positive" and "Strongly Positive" results in the Ide and Harris tests was to seek for light upon the problem of "the doubtful Kahn test"—a problem affecting both serologists and clinicians, especially the latter Our figures, though interesting, are of no real value, again because, without adequate clinical correlation, positive Ide and Harris results by themselves (without reference to simultaneous Kahn results) are of unknown reliability

Conclusions

The following conclusions have been reached after considerable experience of the two tests in a well-equipped and well-staffed serology laboratory, they await confirmation after more extensive use in parallel in small field laboratories

(1) In comparison with the Kahn test, the Harris test is slightly more specific than the Ide test

(2) In the examination of sera from subjects showing evidence of syphilis or yaws, the Harris test is more sensitive than the Ide test

(3) When grades of positivity are introduced, the Harris test is significantly more specific and more sensitive than the Ide test

(4) The Harris test, when used in screening, would be more sensitive than the Ide test

(5) There is no difference in the skill required for the performance of the two tests

(6) The fact that the antigen-suspension in the Harris test can be used up to 24 hrs after mixing (as compared with 10 min in the Ide test) is an advantage in field work

(7) The Ide antigen is simple and inexpensive to manufacture, as compared with the complex and costly Harris antigen

(8) There appears to be no difference in the keeping properties of the two antigens

Summary

(1) The essential points in the techniques of the Ide test and Harris (VDRL) test are described

(2) The results are given of the examination of 8,077 sera from Nigerian subjects by the Ide and Harris tests in parallel with the Standard Kahn test

(3) The Ide test showed a 97 per cent agreement with the Kahn test when testing Kahn-positive and Kahn-negative sera Of Kahn-doubtful sera, 69 per cent gave a positive result with the Ide test The Harris test showed a 99 per cent agreement with the Kahn test when testing Kahn-positive sera, and a 97 per cent agreement when testing Kahn-negative sera Of Kahn-doubtful sera, 77 per cent gave a positive result with the Harris test

(4) The results of the two tests in examining "syphilitic" and "non-syphilitic" sera, and the question of degrees of positivity in the two tests are discussed

(5) The conclusions drawn from a comparison of the Ide and Harris tests are enumerated

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EXTRACT FROM THE ANNUAL REPORT OF THE CHIEF MEDICAL OFFICER FOR THE YEAR 1953*

VENEREAL DISEASES

Syphilis—Though there has been a further fall in the number of patients attending the clinics for the first time with infections of less than one year (see Table B), this fall has been proportionately less than in recent years and in some areas the numbers have actually risen The ratio of male to female patients treated continues to be comparatively satisfactory, having regard to the fact that a high proportion of the men attending dockside clinics were infected overseas Generally speaking, fewer cases of early infectious syphilis are seen among seamen than in 1952, though in London this is less evident and in a few clinics the numbers show a slight rise

EARLY SYPHILITIC INFECTIONS DEALT WITH FOR THE FIRST TIME IN 1952 AND 1953 IN TEN SAMPLE URBAN AREAS

Area	1952			1953		
	Males	Females	Total	Males	Females	Total
London Administrative Area (3 343 000)*	249	95	344	225	44	269
Merseyside (Liverpool, Bootle, Birkenhead, Wallasey) (1 109,830)	130	22	152	78	14	92
Manchester and Salford (875 700)	43	24	67	20	13	33
Tyneside (463 800)	32	18	50	13	15	28
Hull (299,400)	25	16	41	21	16	37
Southampton (177 100)	17	5	22	22	2	24
Bristol (444 200)	25	7	32	22	2	24
Birmingham (1 118 500)	27	12	39	38	13	51
Leeds and Bradford (792 100)	16	10	26	8	5	13
Sheffield (507 600)	1	8	9	14	10	24

* The figures in brackets are the estimated population at 30 June 1953

The figures for infantile congenital syphilis are only slightly less than in 1952 (95 as against 110) and an improvement in this record low number can only be expected if the practice of ante-natal blood testing during each pregnancy becomes more widespread The physician in charge of an important venereal diseases clinic in the north of England reports that such cases as he now sees are almost invariably the children of mothers for whose confinements general practitioners have been responsible, and who have not attended the ante-natal clinics of the local authorities The number of cases of congenital syphilis among older children and adults has fallen from 839 to 749

Though many patients in the later stages of syphilis are treated elsewhere than in the venereal diseases clinics, the clinic figures are of interest in that they show a steep fall in the number of women suffering from latent and what may be called "benign" late syphilis as distinct from those with cardio-vascular or nervous manifestations Many of the former are referred from the ante natal clinics of local authorities, and it may be that the decline in their numbers is not unconnected with the increase in the number of pregnant women under the care of the family doctor and on whom routine blood tests are not usually carried out The fact that there has been no significant fall in neurosyphilis in women and an actual rise in those with cardio-vascular involvement, emphasizes the need for an extension of routine blood testing if these often fatal complications are to be avoided

Condition	Year	Males	Females	Total
Cardio vascular syphilis*	1952	371	131	502
	1953	333	150	483
Neuro syphilis	1952	582	314	896
	1953	546	311	857
All other late or latent stages	1952	1 555	1,867	3 422
	1953	1 337	1 591	2 928
Total late or latent syphilis	1952	2 508	2 312	4 820
	1953	2 216	2 052	4 268

* Patients suffering from cardio vascular syphilis who are also suffering from syphilis of other systems are recorded as suffering from cardio vascular syphilis alone

As well as those attending for the first time in 1953, 17,863 males and 18,580 females remained under treatment or observation for syphilis from former years

Certified deaths in England and Wales from general paralysis of the insane, tabes dorsalis, and aneurysm of the aorta (excluding cases specified as non-syphilitic) are shown in Table E In spite of the fall in the figure for general paralysis of the insane in females, there is little or no significant change in these numbers which serve to some extent as an index of the prevalence of potentially lethal syphilis

Gonorrhoea—There has been a further slight increase in the clinic incidence of gonorrhoea which is due to a rise in the number of new female patients attending the clinics for the first time This rise is

* Part II of the Report of the Ministry of Health for the year ended 31st December 1953 Cmd 9307 p 67 and Appendix C p 250

welcome in that it may indicate a small improvement in the results of contact tracing in this disease

Though there is no certain evidence that penicillin-resistant gonococci are in circulation, there is an impression among some venereologists that relapses are rather less uncommon than they were a few years ago The difficulty, and in many cases the impossibility, of distinguishing relapse from re-infection will be appreciated

Other Venereal Diseases—Three hundred and fifty-six cases of chancroid were seen at the clinics in 1953, as against 403 in 1952, and 76 cases of lymphogranuloma venereum (Nicholas Favre), seven more than in 1952 Two cases of granuloma inguinale (Donovan) were also reported

There has been a marked increase in non-gonococcal urethritis in men, new cases having risen from 11,552 in 1952 to 13,157 in 1953 The investigation and treatment of these patients and their female consorts is time-consuming and often discouraging, as relapse after apparent cure is common It may be significant that the number of women attending the clinics for the first time with various "non-specific" conditions, the majority of whom complain of vaginal discharge, has risen from 8 916 in 1952 to 9,834 in 1953 It is becoming increasingly realized that it is equally important to investigate and treat the female consorts of men suffering from non-gonococcal urethritis as of those with gonococcal infections

The symptoms of non-specific venereal urethritis are often minimal and it is probable that many persons are infected unknowingly and consequently are never treated

Other Conditions treated at the Clinics—There has again been an increase in the number of men as well as women attending the clinics suffering from various conditions with a real or imaginary venereal background These included balanitis, genital "warts," scabies, pediculosis, trichomonas infestation, moniliasis, and other conditions often due to a lack of personal hygiene In addition to 23,400 of these patients a further 36,231 were found only to need reassurance

Therapy—Penicillin continues to be the therapeutic standby for syphilis in all its stages, as well as for gonorrhoea, and there seems little likelihood that it will be superseded by any of the newer antibiotics in the routine treatment of these diseases The new penicillin salts, N, N¹-Dibenzylethylenediamine penicillin (diamine penicillin) and N-benzyl B phenylethylamine penicillin (Benathamine penicillin), which give longer therapeutic blood levels than those obtainable with other preparations, are now under clinical trial in syphilis and yaws If their early promise is fulfilled, they should be of special value in those underdeveloped areas overseas, where a "one-shot" treatment is particularly called for

The treatment of most cases of non-gonococcal urethritis continues to be empirical, though streptomycin, aureomycin, terramycin, and sulphonamides are all more or less successful in shortening an attack, if not always in curing the disease Relapse is all too common and the proper management of the condition cannot be expected until the causal organism or organisms have been identified

Social Aspects—The necessity for social work in venereal diseases clinics is universally recognized, and it should be appreciated that this does not begin and end with the tracing of contacts and defaulters from treatment The clinic doctor rightly spends much of his time explaining the implications of the disease to the patient, allaying anxiety and helping in the solution of the many difficulties, domestic and other, that are inevitably associated with these infections Assistance in this side of his work is just as necessary as is the technical help given by his nursing staff and in most clinics the services of a hospital almoner or one of the health visitors on the staff of the local medical officer of health are available for this purpose It is hoped that in the near future this type of help will be universally attainable

At the request of the Prison Commissioners, the services of a whole-time welfare officer have been made available to the venereologist at Holloway women's prison by the medical officer of health to the London County Council Despite many difficulties, good results have been achieved in tracing the contacts of infected prisoners and in overcoming their reluctance to attend hospital out-patient clinics on discharge Such social work among a section of the population particularly liable to be infected should do much towards reducing an inevitable reservoir of infection

The Present Position—The increased prevalence of venereal urethritis in men and of gonorrhoea in women and also the fact that in some areas the clinic incidence of early infectious syphilis is no longer falling, forbids any complacency and underlines the need for vigilance, especially in seaport cities Here are the main reservoirs of infection, fortunately still half empty, but which would rapidly fill in the event of a national emergency The tracing of contacts, with all its difficulties and disappointments, is now without doubt the most important single measure in the control of the spread of infection

APPENDIX

TABLE A

NUMBER OF CASES (IN ALL STAGES) DEALT WITH FOR THE FIRST TIME AT ANY CENTRE*

Sex	Year	Syphilis	Soft Chancre	Gonorrhoea	Total V D	Other Conditions	Total Attendances
Males	1925	11 782	1 048	24 398	37 228	13 384	1 248 157
	1926	12 118	1 070	25 535	38 723	14 269	1 500 074
	1927	12 393	986	28 195	41 574	16 192	1 621 409
	1928	12 051	1 053	30 425	43 529	17 959	1 794 205
	1929	11 538	1 202	31 810	44 550	17 970	1 958 095
	1930	11 967	1 244	32 217	45 428	19 724	2 119 257
	1931	11 285	1,042	29 310	41,637	19 838	2 251 710
	1932	11 032	845	28 179	40 056	20 745	2 322 982
	1933	10 738	826	29 169	40 733	20 918	2 396 696
	1934	9 615	876	28 787	39 278	23 639	2 488 538
	1935	8 596	1,011	27 506	37 113	23 605	2 474 531
	1936	8 224	880	28 137	37 241	23 393	2 457 595
	1937	8 069	824	29 250	38 143	24 263	2 446 730
	1938	7 832	889	27 947	36 668	26 081	2 218 584
	1939	7 273	827	24 811	32 911	24 324	1 587 111
	1940	7,093	887	21 057	29 037	20 005	1 170 412
	1941	7,790	1 017	20 572	29 379	20 476	1 065 114
	1942	8 529	969	17 956	27 454	22 302	1 071 664
	1943	8 790	773	18 215	27 778	36 868	1 082 427
	1944	7 667	628	16 629	24 924	34 123	973 810
	1945	8 134	589	21 280	30 003	42 110	912 571
	1946	13 803	994	36 912	51 709	70 239	1 279 743
	1947	11 699	776	29 647	42 122	53 766	1 101 970
	1948	9 780	706	25 006	35 492	56 435	995 724
	1949	7 826	543	20 366	28 735	52 526	860 960
	1950	5 979	433	17 007	23 419	55 068	780 451
	1951	4 506	437	14 975	19 918	49 770	677 251
	1952	3 760	389	15 510	19 659	50 353†	650 014
	1953	3 272	347	15 242	18 861	52 414	622 368
Females	1925	7 385	27	6 120	13 532	7 287	470 991
	1926	7 133	21	6 416	13 570	8 082	507 989
	1927	7 553	20	6 809	14 382	8 705	558 298
	1928	7 090	28	7 810	14 928	9 492	628 544
	1929	6 586	22	7 798	14 406	9 595	646 122
	1930	6 916	17	7 939	14 872	10 960	697 938
	1931	6 827	20	7 697	14 544	11 402	741 051
	1932	6 461	29	7 677	14 167	11 586	786 192
	1933	6 029	22	8 583	14 634	11 223	855 627
	1934	5 838	10	8 199	14 047	12 672	918 462
	1935	5 565	16	7 732	13 313	12 625	924 147
	1936	5 128	29	7 715	12 872	13 231	902 733
	1937	5 165	15	7 787	12 967	14 002	895 841
	1938	4 986	15	7 746	12 747	15 182	900 747
	1939	4 605	11	6 489	11 105	14 684	723 455
	1940	4 226	21	5 882	10 129	12 881	597 321
	1941	4 972	20	7 314	12 306	15 068	593 223
	1942	6 542	27	8 413	14 982	20 190	704 076
	1943	7 960	32	10 043	18 035	34 681	868 097
	1944	8 251	28	10 646	18 925	38 566	916 116
	1945	8 508	29	11 603	20 140	41 524	911 974
	1946	10 075	34	10 431	20 540	35 475	864 692
	1947	8 438	27	7 019	15 484	29 314	721 017
	1948	7 349	21	5 306	12 676	27 462	663 503
	1949	5 873	19	4 121	10 013	24 801	595 555
	1950	4 988	17	3 497	8 502	23 840	529 825
	1951	3 926	16	3 089	7 031	21 160	467 412
	1952	3 362	14	3 585	6 961	20 682	427 977
	1953	2 914	9	4 021	6 944	20 452	398 902

*Excludes cases transferred from centre to centre †Including non gonococcal urethritis

TABLE B

CASES OF ACQUIRED SYPHILIS IN TABLE A, WITH INFECTIONS OF LESS THAN ONE YEAR

Year	Number		Per cent of Table A Cases	
	Males	Females	Males	Females
1931	6 421	2 683	56 9	39 3
1932	6 196	2 532	56 2	39 2
1933	5 949	2 141	55 4	35 5
1934	4 888	2 030	50 8	34 8
1935	4 226	1 745	49 2	31 4
1936	4 033	1 642	49 0	32 0
1937	3 986	1 647	49 4	31 9
1938	3 744	1 494	47 8	30 0
1939	3 574	1 412	49 1	30 7
1940	4 029	1 582	56 8	37 4
1941	5 023	2 309	64 5	46 4
1942	5 470	3 576	64 1	54 7
1943	5 159	4 483	58 7	56 3
1944	4 384	4 934	57 2	59 8
1945	5 214	5 527	64 1	64 9
1946	10 705	6 970	77 6	69 2
1947	8 750	5 416	74 8	64 2
1948	6 603	4 034	67 5	54 9
1949	4 392	2 420	56 1	41 2
1950	2 678	1 465	44 8	29 4
1951	1 498	774	33 2	19 7
1952	891	462	23 7	13 7
1953	755	319	23 0	10 9

TABLE C

CASES OF CONGENITAL SYPHILIS DEALT WITH FOR THE FIRST TIME AT THE TREATMENT CENTRES

Year	Under 1 Year	1 and Under 5 Years	5 and Under 15 Years	15 Years and Over	Totals
1931	339	204	974	922	2 439
1932	302	180	857	805	2 144
1933	305	157	774	780	2 016
1934	296	165	708	839	2 008
1935	251	165	671	944	2 031
1936	241	132	600	935	1 908
1937	211	144	534	940	1 829
1938	216	123	448	951	1 738
1939	217	125	406	866	1 614
1940	191	101	357	709	1 358
1941	223	90	321	746	1,380
1942	245	122	309	788	1 464
1943	310	129	348	940	1 727
1944	346	113	271	822	1 552
1945	326	83	210	736	1 355
1946	363	103	215	701	1 382
1947	343	120	214	676	1 353
1948	372	142	215	678	1 407
1949	355	118	197	747	1 417
1950	227	141	203	652	1 223
1951	156	89	198	684	1 127
1952	110	101	191	547	949
1953	95	77	152	520	844

TABLE D

DEATH RATES PER 1 000 LIVE BIRTHS, OF INFANTS UNDER 1 YEAR CERTIFIED AS DUE TO CONGENITAL SYPHILIS

Year	Rate	Year	Rate	Year	Rate	Year	Rate
1912	1 34	1924	0 91	1936	0 24	1948	0 09
1913	1 46	1925	0 82	1937	0 19	1949	0 08
1914	1 55	1926	0 84	1938	0 18	1950*	0 04
1915	1 44	1927	0 77	1939	0 17	1951*	0 03
1916	1 57	1928	0 71	1940	0 16	1952*	0 03
1917	2 03	1929	0 64	1941	0 21	1953*	0 01
1918	1 90	1930	0 55	1942	0 19		
1919	1 76	1931	0 45	1943	0 23		
1920	1 51	1932	0 42	1944	0 16		
1921	1 43	1933	0 35	1945	0 15		
1922	1 12	1934	0 30	1946	0 15		
1923	1 05	1935	0 26	1947	0 09		

Rates for years 1931–1949 are according to the 1940 classification (5th Revision) For 1912–1930 the rates need to be multiplied by the conversion ratio 0 857 for approximate comparability

*For 1950–1953, No 020 2 in International List (6th Revision)

TABLE E

DEATHS FROM GENERAL PARALYSIS OF THE INSANE TABES DORSALIS AND ANEURYSM OF THE AORTA

Years	G P I		Tabes Dorsalis		Aneurysm of Aorta*	
	Males	Females	Males	Females	Males	Females
1911–20	1 697	383	592	106	838	208
1921–30	1 204	277	631	127	860	249
1931–35	819	240	566	125	969	393
1936–39	625	227	471	106	1,017	531
1940–44	482	167	270	71	467	158
1945–49	258	101	157	41	485	166
1946	314	127	178	54	495	156
1947	283	116	164	44	502	177
1948	205	66	111	32	478	169
1949	161	65	114	20	515	191
1950	111	56	99	24	430	225
1951	121	47	111	32	475	204
1952	78	45	100	27	435	222
1953	91	26	87	26	408	190

The averages for the years 1911 to 1939 are based on the 4th Revision of the International List Figures for the years 1940 to 1953 are according to the 6th Revision

Non civilian deaths are excluded from the table from 3rd September, 1939 until 1949 for males and from 1st June, 1941 until 1949 for females

*For years 1911 to 1939 —
Aneurysm (code 96) of the 4th Revision List based on arbitrary rules of assignment

For years 1940 and after —
'Aneurysm of Aorta (code 022) of the 6th Revision List, based on assignment by the certifying medical practitioner Aortic Aneurysm specified as non syphilitic or dissecting is no longer included in this heading

TABLE F

EXAMINATION OF SPECIMENS IN TREATMENT CENTRES AND ASSOCIATED LABORATORIES

Specimens Examined	Microscopical for		Cultural for Gonorrhoea	Serum Tests for		Cerebro spinal Fluid	Other Pathological Investigations
	T pallida	Gonococci		Syphilis	Gonorrhoea		
(*a*) In Treatment Centres	5,822	94 295	2 603	3 393	648	476	35 159
(*b*) Sent by the Treatment Centres for Examination in Associated Laboratories	436	70 312	77 727	291,081	58 152	4 466	18 134

BOOK REVIEWS

Inquérito acerca da Prostituçáo e Doenças venéreas em Portugal, 1950 By A Tovar de Lemos 1953 *Pp* 146, 16 figs Editorial Imperio, Lisbõa

This work, by the Director of the Social Hygiene Dispensary of Lisbon, is based on answers received from health officers throughout Portugal to inquiries on prostitution and the venereal diseases

In 1949 legislation was approved (Law 2,036) which will lead eventually to the end of licensed prostitution and makes compulsory both the notification and treatment of cases of infectious venereal disease Law 2,036 is detailed, it obliges all persons with, or suspected of having, infectious venereal disease to submit to examination and treatment where necessary, and not to expose others to infection Exemption from examination may be secured by a medical certificate attesting to the absence of venereal disease in an infectious stage, but the sanitary authority has the right to submit the suspect to examination by a specialist or to demand a further certificate from a specialist Doctors are obliged to instruct their patients suffering from V D about the gravity of these diseases, and to warn them about exposing others to infection, they must notify infectious cases to the sanitary authority, but names and addresses are to be given only in the case of habitual prostitutes and defaulters from treatment Examination to detect V D is recommended before marriage during pregnancy, at child health consultations, and when blood is grouped Further registrations of prostitutes and the opening of new houses" are forbidden 'Houses' which contravene public health regulations or which constitute foci of infection are to be closed by the sanitary authority It is planned to coordinate, on a national scale the prevention of infectious diseases

The method of the inquiry on prostitution is outlined A questionnaire was sent to Health Officers of each council containing questions on the number of prostitutes in each district, medical inspection, whether the houses" are separate or in designated streets, the number of inmates, police supervision, the estimated numbers of clandestine prostitutes, their places of soliciting, and the measures to control repeated soliciting by minors The results are summarized for each area in Tables with population figures and maps In 1940 there were 5,276 registered prostitutes and 485 'houses" compared with 5,079 and 422 in 1950 There were 133 'houses in Lisbon and six in the Lisbon urban district Registered prostitution is not a problem except in Lisbon Porto, Coimbra, and Évora, for it hardly exists outside these areas, the legislation forbidding new recruitment is intended to bring about its gradual disappearance Clandestine prostitution with its changing forms in modern society is a more difficult problem, most of the registered Lisbon prostitutes began as *clandestinas* The correct approach lies through education and the improvement of economic conditions so that women do not become prostitutes Few prostitutes desire to reform until they cease to earn, and few can liberate themselves from their moral and material disequilibrium The reformed prostitutes must be given work and a place in normal life, if reform is not accepted with good will it always fails

The method of the inquiry on V D is outlined The incidence of cases in each area is recorded as "many", "few", or "rare", and may be compared with the incidence of prostitution, some figures are given Thus, in Mortagua, an area with no significant prostitution, only nine cases of V D have been seen in 15 years and nearly all these represent infections acquired elsewhere The incidence has increased in 37 areas, but is constant or decreasing in the majority Most councils report a greater number of men than women with venereal disease, in nine areas the reverse is true, but no explanation is advanced for this reversal There is evidence of reluctance to seek treatment in some areas Further treatment centres are required in many districts which are listed Law 2,036 is likely to change the conditions revealed by this inquiry

The detailed account of the incidence of prostitution throughout Portugal is of greater value than the section on V D in which few figures are given The effects of Law 2,036 on the problem will be interesting to watch

E D

Modern Diagnosis and Treatment of the Minor Venereal Diseases By Orlando Canizares 1954 *Pp* 131, 19 figs, bibl Blackwell Scientific Publications, Oxford (27*s* 6*d*)

This monograph presents clearly and fully the present state of knowledge regarding the minor venereal diseases, comprising chancroid, lymphogranuloma venereum, and granuloma inguinale It does not deal with non specific urethritis or *Trichomonas vaginalis* infections, or some of the other minor 'conditions commonly dealt with in venereal diseases clinics

The book is a clear and full exposition of standard methods of diagnosis and treatment the differential diagnosis is well presented and the value of advances in chemotherapy is clearly expounded The illustrations are exceptionally good, and the whole format is very attractive There is an extensive bibliography

The monograph will be a valuable reference book for those who rarely meet the conditions described It will be a useful addition to the library of all venereologists and invaluable to doctors in countries where the diseases described occur frequently and prove trouble some

R L

ABSTRACTS

This section of the JOURNAL *is published in collaboration with the two abstracting Journals,* ABSTRACTS OF WORLD MEDICINE *and* OPHTHALMIC LITERATURE, *published by the British Medical Association The abstracts are divided into the following sections Syphilis (Clinical, Therapy, Serology, Pathology, Experimental), Gonorrhoea, Non-Gonococcal Urethritis and Allied Conditions, Chemotherapy, Public Health and Social Aspects, Miscellaneous After each subsection of abstracts follows a list of articles that have been noted but not abstracted All subsections will not necessarily be represented in each issue*

SYPHILIS (Clinical)

Aortic Electrokymogram in Normal Subjects and Patients with Syphilitic Aortic Insufficiency BRANDFONBRENER, M, and EISENBERG, H (1954) *Amer Heart J* 3 figs, 13 refs

Aortic electrokymographic tracings were taken at various points along the aorta in sixty normal subjects and were compared with similar tracings from 33 patients with syphilitic aortic incompetence Records were made of the ascending aorta in the postero-anterior and left anterior oblique positions and of the aortic knob in the former position The records from the two groups differed to a fairly marked degree in contour—for example, a rapidly rising curve with " systolic collapse " was frequently noted in the ascending aortic records from patients with aortic incompetence, and an indistinct dicrotic notch was more common than in those from normal subjects—and to a lesser degree in the time relations of the various phases However, no feature characteristic of aortic incompetence was found which invariably occurred in this condition and in no other condition

It is concluded that as a clinical method in studying the aorta, the electrokymogram would seem to be extremely limited As a physiologic tool, it is crude and certainly would benefit from improvements that would permit calibration for comparison of amplitudes "

William A R Thomson

Painful Aortitis (Des aortites douloureuses) ROUBIER, C (1954) *J Med Lyon*, 35, 741 7 refs

About one-third of all cases of syphilitic aortitis are reported to be accompanied by pain of an anginal type, this being usually attributed to fibrotic obliteration of the coronary orifices Coronary arterial affection, however, does not explain all the cases and the author discusses this problem with special reference to thirty cases of syphilitic aortitis seen by him at Lyons since 1928 in which a detailed histological examination of the heart and great vessels was carried out The clinical, post-mortem, and histological findings in each case are briefly detailed

In thirteen cases (six male and seven female) pain was present during the course of the illness, but was absent throughout in seventeen cases (twelve male and five female), the age range (42 to 72 yrs) was approximately the same in the two groups A fatal termination supervened somewhat earlier in cases in which there was pain, treatment (in the pre-penicillin era) with mercury and bismuth having little effect on the course In general, pain when it occurred was the presenting symptom and usually persisted until death In a few cases, however, there was a gradual diminution in the frequency and intensity of the pain during the course of the disease Two types of pain are described

(1) The classic angina occurring on effort, with typical radiation and relieved by trinitrin,

(2) An atypical anginal pain, usually more severe than (1), often abdominal in site and radiating to the scapulae but never to the arms, occurring at rest, and not relieved by trinitrin

The pathological changes in these cases are described and their role in the causation of pain discussed Thus it was found that obliteration of the coronary ostia occurred in thirteen cases, among which, however, only seven patients complained of pain, two of these having typical angina and five the atypical type of pain Lesions of the coronary arteries themselves, as well as cardiac lesions and obliteration of the origin of the intercostal arteries, were similarly inconstant findings As to the role of lesions of the aorta itself, it was observed that where painful aortitis occurred there was an intense local inflammatory reaction, with a marked peri-aortitis involving the peri-aortic nervous plexus In contrast, in the painless group aortic lesions were confined to the media or made only slight encroachment on the adventitia From this the author, although not denying the importance of involvement of the coronary arteries in producing pain in aortitis, concludes that the existence of an inflammatory peri-aortitis must nevertheless be regarded as a causal factor in some cases

Benjamin Schwartz

Tabetic Charcot's Spine Report of Eight Cases CAMPBELL, D J, and DOYLE, J O (1954) *Brit med J*, 1, 1018 1 fig, 4 refs

Tabetic arthropathy of the spine was first described by Charcot in 1868 but few cases have been recorded in the

Structural and Constitutional Analysis of G P I [In English] POLONIO, P, MENDES, F, GUERRA, M, and SILVA, P (1953) *An port Psiquiat*, **5**, 197 3 refs

Latent Syphilitic Diseases and Their Diagnosis GRILLMAYR, W (1954) *Neurology (Madras)*, **2**, 33 15 refs

Untreated Syphilis in the Male Negro—A Prospective Study of the Effect on Life Expectancy SHAFER, J K, USILTON, L J, and GLEESON, G A (1954) *Publ Hlth Rep (Wash)*, **69**, 684 16 refs

Amyloidosis following Syphilis as a Cause of Death (Amyloidose nach syphilis als todesursache) DAESCHLEIN, G (1954) *Z Haut- u GeschlKr*, **17**, 82 *Bibl*

Syphilis in Quebec in 1952—Developments During the Last 10 Years (La syphilis a Quebec en 1952—Evolution depuis dix ans) GAUMOND, E, and CHARLTON, M (1954) *Laval med*, **19**, 1021 9 figs

Can Syphilis progress in the Presence of Negative Serological Reactions? (Une syphilis peut elle evoluer avec des reactions serologiques negatives?) JOULIA, P, and TEXIER, L (1954) *J Med Bordeaux*, **131**, 951

SYPHILIS (Therapy)

Penicillin Treatment of General Paresis A Clinico-anatomic Study GIANASCOL, A J, WEICKHARDT, G D, and NEUMANN, M A (1954) *Amer J Syph*, **38**, 251 6 figs, 9 refs

The clinical and necropsy findings (including the histology of the brain) in fourteen patients suffering from general paresis who had received only 6 mega units aqueous sodium penicillin within a period of 30 days are reported It is concluded that this dose was adequate to arrest the pathological process of general paresis, any residual lesions being attributable to changes such as neurone destruction which probably anteceded treatment The microscopical findings included persistence of meningeal fibrosis with minimal lymphocytic and plasma-cell infiltration, persistence of a prominent marginal gliosis, persisting evidence of cortical neurone loss, and in many cases minimal to moderate disturbance of the architecture of the cortex Astrocytosis and microglial reaction, including the presence of rod cells, may apparently persist to a slight, and less frequently to a moderate, degree As the interval between treatment and death lengthened perivascular infiltration gradually subsided and the neuropathological findings approached those of inactive paresis until, after 38 months, there were no signs of activity of the syphilitic process in the brain *R R Willcox*

Treatment of Early Syphilis with Chloromycetin MAZZINI, M A, and BLASI, A A (1954) *Amer J Syph*, **38**, 341 7 refs

The authors report, from the University of Buenos Aires School of Medicine, the results of the treatment with chloramphenicol of nine patients with early syphilis In four cases the drug was given in daily oral doses ranging from 40 to 65 mg /kg body weight, and in six cases (one patient was re-treated for re-infection) in doses of 75 to 100 mg /kg, treatment being continued for 6 to 8 days The surface lesions healed rapidly in all cases in the latter group, but of the four cases receiving the lower dosage, healing was delayed in three Serological reversal appeared to be satisfactory The drug was well tolerated in spite of the high dosage, which the authors advise for the type of syphilis encountered in Argentina [Most British doctors would hesitate to use the high dosage of chloramphenicol advocated, but such treatment might be helpful when the patient is intolerant of penicillin] *Robert Lees*

Use of Cortisone during Penicillin Treatment of Secondary Mucocutaneous Syphilis in a Hypersensitive Patient BRODEY, M, and NELSON, C T (1954) *New Engl J Med*, **250**, 1069 1 fig, 12 refs

Attention is drawn to previous papers which have indicated the apparent ability of corticosteroids to suppress the usual response of the host to treponemes and thus promote the spread of untreated syphilitic infection

The article reports a case which during initial treatment of early syphilis showed severe penicillin hypersensitivity He subsequently developed a serological relapse in both blood and C S F, and further penicillin therapy was instituted This resulted in a sensitivity reaction severe enough to warrant the administration of ACTH and cortisone Penicillin was discontinued and chlortetracycline given in an effort to control the syphilitic infection, but 1 year later he developed a dark-field positive mucocutaneous relapse It is suggested that inadequate response to chlortetracycline and possible dissemination of *T pallidum* after cortico steroid therapy may have played an important part in this mucocutaneous relapse

The patient was re-treated with large doses of penicillin while antihistaminics and cortisone were given simultaneously to control the hypersensitivity Some 14 months later his response to treatment was judged satisfactory and there has been a steady decline in serological activity

The authors conclude that providing large doses of penicillin are given to control the syphilitic infection corticosteroids may safely be used to control hypersensitivity in such patients

[It would appear, however that the observation period is as yet too short in view of the previous marked tendency to relapse shown by this patient] *Leslie Watt*

Results of Penicillin, Cortisone, and Non penicillin Treatment of Syphilitic Optic Atrophy, with Report of Clinical Observations KLAUDER, J V and GROSS B A (1954) *Amer J Syph*, **38**, 270 11 refs

This paper reports 104 cases of syphilitic optic atrophy (99 due to acquired and five to congenital syphilis) treated with penicillin, alone or together with other measures and compares the results with those in 86 patients treated before penicillin was available

The first group of 39 patients received 4 2 mega units aqueous penicillin alone, and the same course was given together with fever and metallotherapy to patients requiring re-treatment Favourable progress was noted in 26 cases, while the condition worsened in thirteen, re-treatment being given in seven instances Before treatment the condition was considered to be progressive in 34 of these patients

The second group consisted of 29 patients, in all of whom the optic atrophy was considered to be progressive They were given 6 mega units penicillin and sixteen also received fever therapy (malaria or typhoid vaccine) A favourable response was noted in eighteen cases, while the optic atrophy progressed in eleven, re-treatment was given to six patients

A third group of 36 patients with progressive optic atrophy received eleven mega units penicillin, fourteen receiving fever therapy in addition Metal chemotherapy, more penicillin, and in some instances cortisone or ACTH were given on re-treatment A favourable outcome was noted in 23 cases, while progress was unfavourable in thirteen, eight of which were re-treated

The 86 patients in the " non-penicillin " group received a variety of forms of treatment, including arsenic and bismuth, and in some cases fever and subdural treatment Favourable progress was recorded in 36 cases, while in fifty the condition progressed

[The variations in the regimes of treatment given in the four groups makes any form of strict comparison extremely difficult This paper, however, represents the fruits of a life-time of experience for each, and as such must command respect] *R R Willcox*

Topical Cortisone in the Treatment of Syphilitic Interstitial Keratitis Preliminary Report of 20 Cases (26 eyes) HORNE, G O (1954) *Brit J Ophthal*, **38**, 669 3 refs

In this report the value of topical cortisone in interstitial keratitis is again stressed In only two eyes was there residual corneal scarring sufficient to reduce the vision to 6/18 in one and 6/24 in the other

A G Leigh

Treatment of Interstitial Keratitis with Penicillin or with Penicillin combined with Fever Therapy [In Polish with an English Summary] SEGAL, P, and JASTRZEBSKA, D (1953) *Przegl derm*, **3**, 409

An account of the penicillin treatment of 56 patients (21 female, 35 male) with interstitial keratitis out of 146 cases of congenital syphilis All patients had iritis as well and one had secondary glaucoma Penicillin seemed to be better than the old specific treatments

M H T Yuille

Syphilitic Keratitis and Cortisone (Queratitis sifilitica y cortisona) VILANOVA, X, and DULANTO, F DE (1953) *Actas dermo-sifiliogr (Madr)*, **44**, 374

Good results are obtained but there are strong contraindications Since Woods in 1950 introduced the application in the form of collyrium and ointment locally, these disadvantages have been eliminated

A Arruga

Dangers of Penicillin in the Treatment of Acute Infections in Patients with Undiagnosed Syphilis (Les dangers de la penicilline dans le traitement d'infections aigues chez les syphilitiques meconnus) JUSTIN-BESANÇON, L, KLOTZ, H P, and HAZARD, J (1954) *Sem Hop Paris*, **30**, 3403 1 ref

Penicillin Treatment of Syphilis Part I (Penicillinbehandlung der Syphilis) WERNSDORFER, R (1954) *Z Haut- u GeschlKr*, 17, 236

Findings in the Cerebrospinal Fluid in Secondary Syphilis treated with Penicillin and Bismuth (Reperti liquorali in luetici secondari trattati con penicillina e bismuto) CORTELLA, E (1954) *Rif med*, **68**, 848

Penicillin Treatment of Cardiovascular Syphilis EDEIKEN, J and BEERMAN, H (1954) *Med Clin N Amer*, **38**, 1757 2 figs, 16 refs

What are the Prospects of Modern Anti-Syphilitic Therapy, What is the Critical Stage of the Disease and Why do so Many Divergent Opinions concerning Antibiotical Therapy Exist? [In English] SIMONS, R D G PH (1954) *Ned T Geneesk*, **98**, 3295 28 refs

Treatment and Prevention of Syphilis by Antibiotics HIGUCHI, K, URABE, H, TSUBOI, H, and IWASAKI, H (1953) *Kyushu Mem med Sci*, **4**, 115

Study of Current Treatment Practices in Early Syphilis throughout the World WILLCOX, R R, GUTHE, T, IDSOE, O, and REYNOLDS, F W (1954) *Amer J Syph*, **38**, 388 9 figs, 6 refs

SYPHILIS (Serology)

Use of Calcium Saline Solution in Kolmer Complement-fixation Test KOLMER, J A, and LYNCH, E R (1954) *Amer J clin Path*, **24**, 946 6 refs

The effects of adding calcium to the saline used in the Kolmer complement-fixation test as recommended by Brown and others (*Amer J clin Path*, 1954, **24**, 934) have been examined by the authors at Temple University School of Medicine, Philadelphia Enhancement of the complement titre was found to occur in 78 out of eighty complement titrations, the titres for two full Kolmer complement units in fifty of the tests being equal to or less than the absolute minimum of 1 0 ml of a 1 43 dilution laid down by Kolmer A slight increase in haemolysin titres was also noted

Parallel quantitative Kolmer tests were carried out using saline with and without the addition of 0 04 g $CaCl_2 2H_2O$/litre on 85 syphilitic and 61 non-syphilitic sera and on twelve specimens of syphilitic and 28 of non-syphilitic cerebrospinal fluid (CSF) Stronger reactions were given by 27 syphilitic sera with the added calcium and by six without, while 55 of the non-syphi sera gave negative reactions to both tests, but six sho incomplete lysis of the controls, with possible

positive reactions, in the test with added calcium In the tests on C S F, eight of the syphilitic group gave a stronger reaction with added calcium, and one without, while 23 of the non syphilitic fluids gave negative reactions in both tests, but five showed incomplete lysis of the controls, with some possible false positive reactions, in the test with added calcium

The authors conclude that while the addition of calcium to the saline enhances complement activity and the sensitivity of the Kolmer test, it may be wise to set an arbitrary limit of not less than 0 35 ml of 1 30 dilution of complement as the exact unit, or 1 0 ml of 1 37 dilution as two full Kolmer units, when the test is performed under these conditions If higher dilutions are used incomplete lysis of controls and possible false positive reactions may occur, particularly with C S F

A E Wilkinson

Effect of Calcium Ion on the Kolmer Complement-fixation Test BROWNE, A S, MICHELBACHER, M M, and COFFEY, E M (1954) *Amer J clin Path*, **24**, 934 3 figs, 18 refs

While carrying out the Kolmer complement-fixation test in the laboratories of the California State Department of Health, the authors experienced difficulties due to low complement titres and to fluctuations in titre which could not be explained by variation in the reagents used, but showed a rough correlation with the purity of the distilled water With the addition of calcium to the saline used, however, consistently high and constant titres were obtained, 0 04 g $CaCl_2.2H_2O$ per litre of saline being found to be the optimal level Parallel complement titrations carried out with and without added calcium and with varying periods of primary incubation showed that when primary incubation was omitted altogether the addition of calcium made no difference to the titre, but it increased the titre slightly when incubation periods of 30 min at 37° C and of 16 hrs at 4 to 6° C plus 10 min at 37° C were used With an initial dilution of complement in the two salines of 1 50 instead of the usual 1 30 in the presence of 0 2 ml inactivated normal serum and with a primary incubation period of 16 hrs at 4 to 6° C plus 10 min at 37° C there was less non-specific destruction of complement when calcium was added This was also the case in control tests in which no serum was added With twelve sera the 100 per cent titre (the dilution of complement in 1 ml that just gives complete haemolysis) ranged from 62 to 125 in saline without calcium and from 71 to 125 in saline with calcium In subsequent work the 100 per cent titre was taken as the actual titre found rather than the arbitrary upper limit of 1 43 set by Kolmer

Parallel tests with the two salines on 532 specimens of serum or cerebrospinal fluid (C S F) showed that of 252 (231 sera and 21 C S F) which were reactive to the VDRL slide test, 42 were reactive to the Kolmer test only with added calcium, sixteen sera gave anticomplementary reactions—seven with both salines, seven with added calcium only, and two with Kolmer saline only A comparison of the results of the VDRL slide test with those of the standard Kolmer test on 160,984 sera showed that 4 3 per cent were negative to the latter but reacted to the former In similar tests carried out on 47,701 sera in which calcium was added to the saline and complement used at the titrated dilution this figure was reduced to 3 5 per cent

The authors conclude that the addition of 40 mg CaCl 2H O per litre of Kolmer saline is of value in giving high complement titres, increasing sensitivity, and stabilizing the test results Magnesium should be added as the chloride instead of the sulphate to avoid precipitation of calcium sulphate *A E Wilkinson*

Anticomplementary Reaction in Syphilis Serodiagnosis GELPERIN, A (1954) *Amer J Syph*, 38, 304 10 refs

The phenomenon of the anticomplementary reaction in complement-fixation tests is neither absolutely preventable nor completely understood From investigations carried out by the authors at Johns Hopkins University and Hospital, however, it is evident that positive serum is made anticomplementary by the addition of the alcoholic extract of normal human serum Eagle's routine Wassermann technique revealed no haemolytic factors, nor were the prepared antigens in themselves anticomplementary The authors experiments also indicate that while benzene has no effect, the addition of ether makes serum lipids 'available" as antigen, cholesterol merely acting as a 'fortifying' agent The author considers that syphilitic serum contains the ingredients necessary to complete an antigen antibody reaction He also assumes that the anticomplementary phenomenon may result from the mobilization of the serum lipids and their consequent availability as an antigen, and that this mobilization is in some way produced by treating the serum with ether

G L M McElligott

Victoria Blue (Berger-Kahn) Flocculation Test for the Serological Diagnosis of Syphilis GREENBURGH, H and STEPHENS, B J (1954) *Guy's Hosp Rep* **103**, 174 6 refs

The Victoria blue (V B Berger Kahn) flocculation test for the diagnosis of syphilis first described by Berger (*J Path Bact* 1943 **55**, 363) is a slide test of relatively simple technique in which the dye Victoria blue 4R is used as a sensitizing agent and as an indicator of the occurrence of flocculation when serum from a syphilitic patient is added to a mixture of compound tincture of benzoin and Kahn antigen

The authors applied this test in parallel with the Wassermann and Kahn reactions to all sera sent to the clinical pathological laboratory of Guy's Hospital London for routine testing for syphilis during the first 5 months of 1950, during which time 2 116 samples of serum were tested Complete agreement between the three tests was obtained in 1 845 cases (87 2 per cent) In 162 instances the V B test gave a doubtful (±) result with sera from patients with no clinical evidence of syphilis and with which the Wassermann and Kahn tests were negative It was decided, therefore to classify doubtful V B -test results as negative and to accept only

a positive result (+) or greater degree (++) as indicating a positive reaction to the test This gave complete agreement between the three tests in a further 7 65 per cent of cases, giving a total of 94 85 per cent with full agreement [Doubtful Wassermann reactions were, however, classed as positive]

In no instance was it found that an untreated case of confirmed syphilis gave a negative result with the V B test Negative V B -test results were found in association with positive Wassermann and/or Kahn reactions in 34 instances In only twelve of these cases did further investigations lead to a diagnosis of syphilis, and all twelve patients had received antisyphilitic treatment In another group of 26 sera giving positive V B -test results in the presence of negative Wassermann and Kahn reactions it was found that five samples of serum were from cases of early untreated syphilis, three from cases of late untreated syphilis, fifteen from cases of treated syphilis, and one from a case of general paralysis in the remaining two cases no information was available

The authors conclude that the V B test, on account of the stability of the antigen, the small amount of serum required, and the ease and rapidity with which the test can be carried out, is very suitable for use in laboratories where large numbers of sera have to be screened for evidence of syphilis They recommend that sera giving a positive reaction should be further examined by other tests in order to confirm the result and eliminate false positive reactions

A J King

Comparative Reactivity of the VDRL Slide and Other Tests for Syphilis in Random Population Groups (including *Treponema pallidum* Immobilization Test) Harris, A Olansky, S , and Bossak, H N (1954) *Amer J Syph* , **38,** 295 14 refs

From 19 591 blood specimens collected from volunteer donors 2,560 random samples were tested for syphilis at the Venereal Disease Research Laboratory of the U S Public Health Service by four slide microflocculation methods using cardiolipin-type antigens namely, the VDRL slide, Kline Standard, Rein-Bossak, and Mazzini tests In 52 cases the results were not in agreement and the residual serum from these specimens was subjected to the *Treponema pallidum* immobilization (TPI) test A direct comparison of the VDRL slide and TPI tests was also made on 466 specimens The results of these comparisons [which are well tabulated] suggest

(1) that the VDRL slide test is rather less sensitive than the other three serum tests

(2) that a positive result in the TPI test combined with a negative result in the VDRL slide test is probably a more frequent discrepancy than the reverse ,

(3) that not one of the five tests used supported the clinical findings or the history in 100 per cent of cases

G L M McElligott

Cardiolipin Antigen in the Kolmer-Wassermann Test for Syphilis Klein S J , Konwaler, B E , and Leiby, G M (1954) *Amer J Syph* , **38,** 318 31 refs

In this article the authors record a comparison of cardiolipin antigen with standard Kolmer antigen in the Kolmer-Wassermann reaction Parallel testing was carried out on 374 sera from known cases of syphilis, and on 2,956 unclassified sera on 518 presumed non-syphilitic sera, and on 1,882 unclassified sera Though cardiolipin antigen gave a significantly higher incidence of false positive reactions in the non-syphilitic sera, in general it gave results which correlated better with a history of syphilis, especially in low titre, than the Kolmer antigen This was also the case in the unclassified sera

The results of a large-scale screening of 40,010 unclassified sera with the Kline and Kahn tests are also reported These showed the more sensitive Kline test to be more efficient for screening purposes than the Kahn test in spite of the latter being more specific

G L M McElligott

Immune-Adherence Test for Syphilis Comparison with TPI and VDRL Slide Tests Olansky, S , Harris, A , and Casey, H (1954) *Publ Hlth Rep (Wash)*, **69,** 521 8 refs

The immune-adherence (IA) test (Nelson, *Science*, 1953, **118,** 733) was carried out on 234 syphilitic and 71 presumed non-syphilitic sera at the Venereal Disease Research Laboratory of the U S Public Health Service, and the results compared with those of the treponemal immobilization (TPI) test and the VDRL slide test using cardiolipin antigen As no criteria of positivity have yet been laid down for the IA test, the sera were divided into three zones of reactivity according to the treponeme count (*a*) 0 to 10 treponemes per 10 fields , (*b*) 11 to 30 , and (*c*) 31 or more

Of 44 sera from patients with primary and 54 from patients with secondary syphilis, including both treated and untreated cases, more were placed in Zone A or B than gave a positive result in the TPI or VDRL tests The IA and TPI tests were similar in that the results of both sometimes remained positive in an adequately treated case longer than that of the VDRL test Closer agreement was found between the results of the three tests on sera from 74 patients with latent syphilis and 62 with late syphilis again including treated and untreated cases This may be accounted for by the small proportion of patients who had had adequate treatment and by the fact that in the majority of these cases less than 6 months had elapsed between the completion of treatment and the examination of the serum so that positive reactions to the VDRL slide test would be expected

The 71 patients who were presumed to be non-syphilitic included several [number not stated] whose sera had previously shown some reactivity to one or more serological tests for syphilis, but who were thought to be non-specific reactors because of the lack of clinical evidence or history of syphilis In the whole group, six gave Zone-A reactions to the IA test, nine gave a positive reaction to the TPI test, and nine gave a positive reaction to the VDRL test

From an analysis of these results it is concluded that the two tests in which treponemal antigens are used may give divergent results with the same serum, and that maximal (Zone-A) reactions with the IA test may be

obtained in some cases where there is no other evidence of syphilis The authors also conclude that the substance responsible for reactivity to the IA test is probably similar to, if not identical with, that responsible for reactivity to the TPI test, and that the IA-test results follow those of the TPI test more closely than those of the VDRL test As the IA test is simple and does not need a freshly prepared antigen, it may provide a practical substitute for the TPI test

[The high incidence of positive reactions with all three tests among the " presumed non-syphilitic " group makes it difficult to assess the specificity of the IA test from this material]

A E Wilkinson

Relation between the Quantitative Kahn and Wassermann Reactions and the Erythrocyte Sedimentation Rate (Das Verhalten von quantitativer Kahn- und Wassermann-Reaktion und Blutkorperchensenkungsgeschwindigkeit) KITTSTEINER, W (1954) *Arch Derm Syph (Berl)*, **198**, 23 5 figs, 5 refs

Investigation into the cause of the well-known variability of the titre in serial serological tests for syphilis on individual patients, even when laboratory techniques, reagents, and treatment are kept as constant as possible, suggested that there was some correlation between the titre and the erythrocyte sedimentation rate (E S R) This was proved to be statistically significant for the Kahn and Wassermann reactions and to be of particular importance in cases in which the E S R is either very low or very high Some examples, with statistical evaluation, are given

[This is an interesting line of research It is not clear from the paper whether the abnormal E S R was thought to be due to syphilis or to other causes]

G W Csonka

Experience with the Cardiolipin Complement-fixation Reaction I Analysis of the Results of 62,910 Serological Tests for Syphilis (Erfahrungen mit der Cardiolipin-Komplementbindungsreaktion 1 Auswertung der Ergebnisse von 62910 serologischen Luesuntersuchungen) LEGLER, F (1954) *Z Hyg InfektKr* , **140**, 87 Bibl

Between 1950 and 1953, 62,910 sera were examined for syphilis at the State Bacteriological Research Institute, Erlangen, seven different tests being employed These were the cardiolipin-complement-binding reaction (CCBR) (using cardiolipin as antigen), three types of the Wassermann reaction (with syphilitic liver, human heart, and calf heart extract as antigens), the citochol ' reaction, the Meinicke II test, and the Kahn test The greatest number of strongly positive results were obtained with the cardiolipin test (Kolmer technique), followed in order by the Meinicke II test, the citochol reaction, and the Kahn test The CCBR was alone positive in 2 244 samples of serum, most of which came from old, treated cases, whereas the Wassermann reaction using the other antigens was alone positive in 949 cases, most of which, however, were thought to be non-syphilitic

G W Csonka

Reproducibility of Results of the TPI Test BOAK, R A, MILLER, J N, and CARPENTER, C M (1954) *Amer J Syph*, **38**, 434 5 refs

Although in some hands the *Treponema pallidum* immobilization test has failed to give consistent results on repetition in a high proportion of cases, the results in 97 4 per cent of 874 specimens tested and re-tested by the authors were in complete agreement Though no certain explanation can be given for the few disagreements, the possibility that many patients with no history of treatment for syphilis may nevertheless have received antibiotics for other diseases cannot be eliminated The necessity for extreme care in cleansing the glass ware used in the test is emphasized

G L M McElligott

Suitability of Heparinized Plasma and Deheparinized Serum in Serodiagnostic Tests for Syphilis REIN, C R, SCHWARTZ, S, and KELCEC, L C (1954) *Amer J Syph*, **38**, 405 3 refs

The purpose of this study reported from the New York University Hospital was to determine the suitability of heparinized human plasma for examination by the standard serological tests for syphilis The heparinized specimens were converted to serum by adding 0 1 ml (2 5 mg) protamine sulphate to each ml plasma, the tubes then being inverted several times, a clot developing within 10 min It is stated that although the serological activity of serum so prepared from heparinized plasma is apparently not impaired, microflocculation tests may be interfered with by a precipitate which appears on heating and which needs prolonged centrifugation for its complete removal, it was also noted that turbid reactions are obtained in complement-fixation tests Heparinized plasma is thus less satisfactory than serum for serological testing

G L M McElligott

Comparison of Spinal Fluid Findings among Syphilitic and Nonsyphilitic Individuals CUTLER, J C, BAUER, T J, PRICE, E V, and SCHWIMMER, B H (1954) *Amer J Syph*, **38**, 447 3 figs, 9 refs

Cerebrospinal fluid obtained at the Chicago Intensive Treatment Center from 346 normal subjects 293 patients with primary syphilis, and 477 patients with secondary syphilis were examined by the authors the Kahn test a cell count, and an estimation of the protein content by the modified Denis-Ayer method being carried out at the Venereal Disease Research Laboratory, Staten Island, New York In a second series the Kolmer complement-fixation test and the Eagle flocculation test were performed in place of the Kahn test on specimens of fluid obtained at the U S Public Health Services Hospital, Staten Island, from 215 normal subjects 210 patients with primary syphilis and 83 patients with secondary syphilis In both series the patients were untreated at the time of examination

In the Chicago series none of the specimens from cases of primary syphilis reacted with the Kahn test, while ten (2 per cent) of the secondary cases did so In

the Staten Island series eight patients with primary syphilis (3 7 per cent) and 24 with secondary syphilis (22 4 per cent) gave a positive reaction with the Kolmer test These differences were possibly due to variations in race and sex distribution between the two series and to differences in the sensitivity of the serological tests used

No differences were found in the cell count in the Chicago series between normal subjects and patients with primary or secondary syphilis where the serological reactions were negative in the spinal fluid Of the normal subjects the cell count was greater than 10 per c mm in 2 3 per cent , whereas in the Staten Island series only one (0 5 per cent) had a count above this level Where the serological reactions were positive in the spinal fluid the corresponding figures were 75 and 21 9 per cent at the two centres respectively

In the Chicago series a protein concentration of more than 40 mg /100 ml was found in 15 1 per cent of specimens from normal subjects, in 17 4 per cent of those from cases of primary syphilis, and in 11 5 per cent of those from cases of secondary syphilis where the serological reactions were negative in the spinal fluid The corresponding figures for the Staten Island series were 35 3, 13 3, and 9 per cent respectively The authors consider that in the absence of positive serological reactions in the spinal fluid the total protein content alone, as measured by the Denis-Ayer method, is of little significance in indicating involvement of the central nervous system in early syphilis Some patients who had shown high protein levels were re-examined a year after presumably successful treatment, and the level was maintained in 31 out of 45 patients The authors suggest that this may be normal for some individuals

[The ' normal " subjects with cell counts and protein levels outside the accepted normal range were not, apparently, investigated further to exclude possible causes for these findings The paper contains a mass of data in tabular form which cannot be compressed into an abstract, but which merits attention by those called upon to interpret spinal-fluid findings in early syphilis] *A E Wilkinson*

Treponemal Immobilization and Standard Test Reactions in Suspected Biologic False Positive Sera WHEELER, A H , GOOR, K VAN, and CURTIS, A C (1954) *Amer J Syph* , 38, 437 17 refs

The treponemal immobilization (TPI) test has been carried out at the University of Michigan Medical School on 763 sera from patients in whom the standard tests for syphilis (STS) had been found positive at other laboratories The TPI test gave positive results in 370 cases, negative in 338, and doubtful in 25

A tentative clinical diagnosis of syphilis had been made in 116 cases, and the TPI reaction was positive in 81 of these, while of 256 patients who were thought to be non syphilitic and to have given a non-specific reaction to the STS the TPI reaction was positive in 92 In seventy of these patients the history of non-specific reaction was of long duration , in 34 of the seventy in whom a suspected predisposing factor, such as lupus erythematosus or malaria, was present the TPI reaction was negative , of 36 in whom no such cause was evident, however, it was negative in only fifteen The presumed non-specific reaction was thought to be of the acute type in 186 patients , these included 42 patients with upper respiratory tract infections, in 33 of whom the TPI reaction was negative, and eleven patients in whom the reaction had followed immunization [agent not stated], in nine of whom the TPI reaction was negative, as it was in 29 out of 39 sera from pregnant women [This is a considerably higher incidence than other workers have found in pregnancy sera]

An estimate of the reproducibility of the result of the TPI test was made from the results of examinations of second specimens of serum from 42 patients Identical results were obtained in 33 cases, there were minor discrepancies in seven, and in two cases in which the result was initially positive subsequent tests gave negative results More than one test was made on the same specimen of serum in 195 cases, identical results being obtained in 154 , in eight an initial doubtful result was found to be definitely positive or negative on re-testing, and one serum which originally gave a positive reaction was found negative at the second test , 32 sera were either anticomplementary or toxic when first examined The authors conclude that the TPI test gives satisfactory reproducibility of results *A E Wilkinson*

Value of Merthiolated Sera in Evaluation Surveys REIN, C R , and KELCEC, L C (1954) *Amer J Syph* , 38, 308 8 refs

" Merthiolate " (sodium ethylmercurithiosalicylate) is an excellent bacteriostatic and bactericidal agent for the preservation of sera It has been found to be of value in evaluating serodiagnostic tests for syphilis It is also of value in preparation of positive control sera and for the shipment of sera from distant places to a central laboratory for serologic testing —[*Author's summary*]

Three Years' Practical Experience of the Treponemal Immobilization Test (Nelson and Mayer's Method) (Trois annees de pratique du test d'immobilisation du *Treponema pallidum* (methode de Nelson et Mayer)) VAISMAN, A , HAMELIN, A , and VAISMAN, H (1954) *Presse med* , 62, 1074 23 refs

The authors discuss the practical aspects of the *Treponema pallidum* immobilization (TPI) test on the basis of their experience in the performance of 7,922 tests at the Alfred-Fournier Institute, Paris, during 1951–53

In sero-negative primary syphilis the TPI test result was invariably negative before treatment, but in the majority of cases became positive later, this positivity persisting in some instances up to 18 months in spite of negative results of standard tests and of adequate treatment In sero-positive primary cases and in secondary cases the TPI reaction became positive later than did other reactions and remained so for much longer It is suggested that the performance of this test after several years might prove useful in confirming the efficacy of treatment

In cases of clinical tertiary syphilis, asymptomatic latent syphilis, and cases insufficiently or irregularly treated, as well as in those in which there was clinical or serological relapse, the TPI reaction was invariably positive and remained so after the other reactions had become negative as the result of treatment Similar results were obtained in tests of both blood and cerebrospinal fluid in cases of tabes dorsalis and general paresis The reaction was also positive in all cases of congenital syphilis Attention is drawn, however, to the possibility of a passive transfer of antibodies from a serologically-positive mother in neonatal cases giving a positive reaction which subsequently becomes negative

Of the 7,922 samples of serum examined 265 (3 35 per cent) were considered to have given false positive reactions to the standard tests, these reactions being feeble or variable as a rule In case of re-infection formation of antibodies was more rapid than in first infections and the TPI reaction became positive earlier The authors claim that a positive TPI reaction is the most reliable evidence of the presence of a recent or old syphilitic infection, antibodies never having been found in normal subjects or in any disease other than the treponematoses Because of the long duration of positivity the TPI test allows of retrospective diagnosis of syphilis in treated cases, and a negative test result after treatment is probably the most reliable criterion of cure They point out that the persistence of immobilizing antibodies does not necessarily indicate active disease

Benjamin Schwartz

Culture of *Treponema pallidum* and the Immunological Diagnosis of Syphilis (Pallidakultur und Immunodiagnostik der Syphilis) SCHERESCHEWSKY, J (1954) *Z Haut- u GeschlKr* , **17**, 233

Experience with De Donno's Proposed Modification of the Wassermann Reaction (Esperienze con il nuovo metodo per la reazione Wassermann proposto da De Donno) VALERIO V , and FRANCIOSI, A (1954) *Rif med* , **48**, 1160

Obstetrical Significance of the Treponemal Immobilization Test of Nelson and Mayer (Interet du test d immobilisation du treponeme de Nelson et Mayer en milieu obstetrical) PIGEAUD, H SOHIER, R , THIVOLET, J , RICHARD, G , and ROLLAND, M (1954) *Ann Med* , **55**, 393 Bibl

Specificity and Sensitivity of the Cardiolipin Macroflocculation Reaction (Zur Spezifitat und Empfindlichkeit der Cardiolipin-Mikroflockungsreaktion) BOLLINGER, D (1954) *Dermatologica (Basel)*, **109**, 75 21 refs

Comparison of the Ide Test with the Kahn Test and the Interpretation of the Ide Test BOULGER, L R , and WINSTON, R M (1954) *W Afr med J* , **3**, 130 4 refs

Behaviour of the Serum Reactions for Syphilis after Treatment with Penicillin (Das Verhalten der Blutserumreaktionen auf Syphilis nach einer Penicillin behandlung) GUMPESBERGER, G (1954) *Z Haut- u GeschlKr* , **17**, 170 9 refs

Interpretation of Positive Serologic Tests for Syphilis in Clinically-negative Patients MAGNUSON, H J (1954) *J Mich med Soc* , **53**, 744 5 refs

Personal Experience of Cardiolipin in the Sero diagnosis of Syphilis (La nostra esperienza con la cardiolipina nella sierodiagnosi della lue) MARSON, G B , and ROSSETTI, C (1954) *Minerva derm (Torino)*, **29**, 353 29 refs

Relation of Lymphogranuloma Venereum to Syphilis and to False Positive Serologic Tests for Syphilis SIMPSON, R G (1954) *Amer J Syph* , **38**, 422 32 refs

False Positive Syphilitic Reactions in Leprosy with special reference to the Cardiolipin Antigens (Le false reazioni per la lue nella lebbra con particolare riguardo per gli antigeni alla cardiolipina) LOMUTO, G (1954) *Minerva derm (Torino)*, **29**, 255 22 refs

SYPHILIS (Pathology)

Preliminary Report on Comparative Investigations on Patients with Framboesia and Syphilis by means of the Luotest and Framboetin Skin Tests (Vorlaufige Mitteilungen uber vergleichende Untersuchungen an Frambosiekranken und Luetikern mit den beiden Hauttesten Luotest und Frambotin) GRILLMAYR, W , ROTTMANN, A , and TEICHMANN, J (1954) *Wien med Wschr* , **104**, 996

Spinal Fluid Evaluation in Neurosyphilis RAUSCH, N G (1954) *N Y St J Med* **54**, 2708 10 refs

SYPHILIS (Experimental)

Studies on the Metabolism of the Treponemata I Amino Acid Metabolism BARBAN, S (1954) *J Bact* , 68, 493 3 figs 14 refs

Free Amino Acids and Glutathione of Normal and Syphilitic Rabbit Testes TAUBER H *(1954) Proc Soc exp Biol (N Y)*, 86, 838 1 fig , 5 refs

Studies on the Mechanism of Action of Cortisone in Experimental Syphilis TURNER, T B and HOLLANDER, D H (1954) *Amer J Syph* , 38, 371 5 figs, 23 refs

GONORRHOEA

Question of the Penicillin Sensitivity of Gonococci (Zur Frage der Penicillinempfindlichkeit der Gonokokken) MARCUSE K , and HUSSELS, H *(1954) Derm Wschr* , **130**, 1031 1 fig 22 refs

At the County Medical Research Laboratories Berlin the sensitivity to penicillin of gonococci obtained from

cervical and urethral smears in 232 cases of gonorrhoea was investigated between 1950 and 1952. By dividing cultures into a number of subcultures various degrees of resistant gonococci were grown, the authors' methods are described in detail. The limit of penicillin sensitivity was reached at a concentration of 0·06 unit penicillin per ml medium, at which level no growth was obtainable. When such cultures were allowed to continue growing the gonococci always reverted to a more sensitive strain, this biological characteristic is thought to explain the fact that no penicillin-fast gonococci have so far been found. The authors believe that there is little likelihood of such a change occurring.

G W Csonka

Oral Tetracycline Hydrochloride for the Treatment of Acute Gonorrhoea in Males. Metzger, W I, Marmell, M, Prigot, A (1954) *Amer J Syph*, **38**, 480. 2 refs.

The newly developed antibiotic tetracycline is readily absorbed and widely diffused throughout the body, in particular it is excreted in high levels in the urine, a finding which the authors consider is of great importance in treating infections of the genito-urinary tract such as gonorrhoea.

At Harlem Hospital, New York, fifty male patients suffering from acute gonorrhoea were treated with a total dosage of 1·0 g. tetracycline. Cure resulted in 44 cases, a cure rate of 88 per cent. This was not quite so good as that obtained with chlortetracycline (aureomycin) in a comparable series, in which the cure rate was 94·3 per cent. In another group of 24 patients suffering from the same complaint and treated with a total dosage of 1·5 g. tetracycline there were no failures, a cure rate of 100 per cent. No drug toxicity was observed in any of the patients.

Neville Mascall

Relapses after the Treatment of Gonorrhoea with Penicillin (Ruckfalle nach Penicillinbehandlung der Gonorrhoe). Fruhwald, R (1954) *Z Haut- u Geschlkr*, **16**, 278.

The incidence of relapse after treatment for gonorrhoea by the various methods used successively at the Municipal Clinic, Zwickau, Germany, during the last 30 years in a total of 1,574 men and 3,959 women is given as follows, only those relapses being accepted as such which occurred during the patient's stay in hospital.

Treatment	Men			Women		
	No Treated	Relapsed		No Treated	Relapsed	
		No	Per cent		No	Per cent
Local therapy	177	15	8·5	205	66	32·2
Sulphonamide	331	55	16·6	587	61	10·4
Intramuscular penicillin	1 829	95	5·2	2 344	46	1·9
Oral penicillin	237	29	12·7	823	30	3·6

Although the majority of cases relapsing after treatment with penicillin had received it in low dosage, some had received as much as 600,000 units. In about 20 per cent of cases the relapse was detected only after the tenth microscopical examination, and it is stressed that frequent and prolonged observation is necessary before a patient can be regarded as cured.

[The value of this paper would have been much greater if details had been given of the type of penicillin used, the antibiotic sensitivity of gonococci in the relapse cases, and the results of re-treatment, and above all if it had been stated whether the proportion of relapses after penicillin treatment is on the increase. The very low incidence of relapse in women after oral or parenteral treatment with penicillin compared with that in men is remarkable.]

G W Csonka

N N′-Dibenzylethylenediamine Dipenicillin G Given Orally for the Treatment of Gonorrhea. Willcox, R R (1954) *Amer J Syph*, **38**, 469.

The results of treatment of 74 patients suffering from gonorrhoea with N N′-dibenzylethylenediamine di-(benzylpenicillin) given orally in a flavoured syrup base are reported. In 46 cases single oral doses ranging from 600,000 units to 4·8 mega units were given, the remaining 28 patients receiving two doses, each of 2·4 mega units, at an interval of 6 hrs.

Of the former group, 44 were followed up for periods up to 201 days. Of these, sixteen were definite failures, seven were considered to be cases of re-infection, three more had non-specific infections, and only eighteen (40 per cent.) could be regarded as cured. Of 23 out of the 28 given two doses and followed up for a maximum period of 177 days, fourteen (60 per cent.) "had no subsequent incident", and four were definite failures.

It is concluded that this product given in single orally-administered doses of up to 4·8 mega units is of little value in the treatment of gonorrhoea. The results of giving two doses of 2·4 mega units at an interval of 6 hrs were somewhat better.

Neville Mascall

Effects of the Administration of Erythromycin upon *Neisseria gonorrhoeae* and Pleuropneumonia-like Organisms in the Uterine Cervix. Rubin, A, Somerson, N L, Smith, P F, and Morton, H E (1954) *Amer J Syph*, **38**, 472. 15 refs.

In the 5-year period 1935–40 before penicillin was available the average number of reported cases of gonorrhoea in the United States was some 175,000 per year, in the last 5 years the figure has been about 200 000 per year. In view of this continuing incidence of gonorrhoea and the ill health due to its sequelae (notably chronic pelvic inflammatory disease) the authors, working at the University of Pennsylvania, Philadelphia, decided to test the efficacy of the newer antibiotic erythromycin, which is reputed to be effective against organisms resistant to other antibiotics. In discussion they also point out that it may be significant that other investigators have isolated pleuropneumonia-like organisms (PPLO) from the uterine cervix of approximately 80 per cent of women suffering from gonorrhoea. Erythromycin to a total dose of 3·6 g. was administered orally to 24 female out-patients with gonococcal infection,

confirmed by isolation of the organism, three 100-mg tablets being taken four times a day for 3 days In 22 cases (92 per cent) cultures for the gonococcus were negative, and remained so in eighteen cases for three successive weeks, of the two unsuccessful cases, in one the organism was still present after treatment and in the other it reappeared after an interval of 2 weeks None of the patients developed signs or symptoms suggestive of gonorrhoea of the upper genital tract Erythromycin had no discernible effect on PPLO Before treatment eighteen patients (75 per cent) had both gonococci and PPLO present in the cervix, and after treatment PPLO could still be isolated in sixteen of them (67 per cent) Side-reactions occurred in nineteen (79 2 per cent) of the patients, in the form of diarrhoea, abdominal cramps, nausea, and vomiting, and sixteen patients developed temporary vulvar or anal itching, but in no instance were the symptoms severe enough to require discontinuation of therapy

Neville Mascall

Successful Treatment of Gonorrhoeal Ophthalmitis by Sintomycin [In Russian] ZOLOTAREVA, M M (1954) *Vestn Oftal*, 33, 44

Prevention of Ophthalmia Neonatorum (Profilaxia da oftalmia do recemnasoido) DE MORAES, A (1953) *An brasil Ginec*, 36, 283

Oral Penicillin with and without Benemid in the Treatment of Gonorrhea JACOBY, A, POLLOCK, J, and BOGHOSIAN, V (1954) *Amer J Syph*, 38, 478 3 refs

Incidence of Gonorrhoeal Complications [In English] OLIN, T E (1954) *Ann Chir Gynaec Fenn*, 43, Suppl 5, 279 9 refs

Investigation with Gonococcal Cultures into the Question of the Existence of an Antagonism between PAS and Sulphonamides (Untersuchungen an Kultur-Gonokokken zur Frage des Bestehens eines Paraaminosalicyl-saure-Sulfonamid-Antagonismus) ZIERZ, P, and PAETZOLD, O H (1954) *Hautarzt*, 5, 363 6 refs

Chemotherapy of Gonorrhea Clinical Observations in 201 Cases MENDELL, H E, WORNAS, C G, and FOXWORTHY, D L (1954) *Tex St J Med*, 50, 649 7 refs

NON-GONOCOCCAL URETHRITIS AND ALLIED CONDITIONS

Investigations into the Pathogenicity of Pleuropneumonia-like Organisms in the Urogenital Tract in Man, with special reference to Non-Specific Urethritis (Untersuchungen zur Pathogenität der pleuropneumonieahnlichen Organismen im Urogenitaltrakt des Menschen mit besonderer Berucksichtigung der unspezifischen Urethritis) ROCKL, H, NASEMANN, T, and STETTWIESER, E (1954) *Hautarzt*, 5, 340 8 figs, bibl

At the University Dermatological Clinic, Munich, examination of the urogenital secretions of 443 patients for the presence of pleuropneumonia-like organisms (PPLO) gave the following results Of 115 specimens from men who had never had any urogenital disease, 22 (19 1 per cent) gave a positive culture, and of 120 specimens from men with non specific urethritis, 32 (27 per cent) were positive Of twenty cases of chronic prostatitis, the prostatic secretions were positive for PPLO in three (15 per cent) Culture of cervical or urethral scrapings from 117 apparently healthy women was positive for PPLO in 73 instances (62 per cent), and of 31 urethral specimens from healthy children of both sexes, four were positive

The authors point out that the difference between the results in men with non specific urethritis and those in controls is insignificant, and from these as well as the other findings they conclude the PPLO are normal inhabitants of the urogenital tract The possibility of the organisms assuming pathogenicity at certain times, however, is not altogether dismissed

G W Csonka

Erythromycin in Non-Specific Urethritis WILLCOX, R R (1954) *Lancet*, 2, 684 8 refs

The antibiotic erythromycin (prepared from *Streptomyces erythreus*) has given varying results in the treatment of gonorrhoea and granuloma inguinale and it also shows some potency against syphilis, but none against lymphogranuloma venereum Pleuropneumonia-like organisms, which have often been incriminated in non-specific urethritis, are highly resistant to erythromycin, a number of workers, however, have recently tended to discount the role of these organisms in the causation of urethritis

At St Mary's Hospital, London, the author has treated 25 men with previously untreated non specific urethritis with a deliberately low dose of erythromycin (100 mg four times daily for 6 days, a total dose of 2 4 g) In the majority of cases the urethral discharge promptly disappeared, but of 21 cases followed up, seven (33 3 per cent) required re treatment most of these being patients whose discharge had been present for 9 days or more Mildly toxic effects of the drug were shown by looseness of the bowels in most patients with frank diarrhoea in three cases while headache pain round the heart, and heartburn were also noted

The author regards erythromycin as clearly beneficial in the treatment of non specific urethritis, and deduces that such action is an added argument against pleuropneumonia like organisms being a cause of the disease

[So many agents have been shown to cause non specific urethritis, and such a variety of treatments has been advocated in the past few years that it is too early to acclaim erythromycin as other than a possibly useful adjunct to the pharmacopoeia The number of cases here reported is too small to carry conviction, and the failure rate of 33 3 per cent does not compare favourably

with the results obtained with oxytetracycline, as described by the author in a previous communication (*British Journal of Venereal Diseases*, 1953, **29**, 225)]
Douglas J Campbell

Arthritis with Simultaneous Suppurative Conjunctivitis and Urethritis (the so-called Reiter's Syndrome) treated with Post-insulin Light Hypoglycaemic States [In Polish] DAWIDOWICZ, A (1953) *Pol Tyg lek*, **8**, 1700 14 refs

Local Treatment of Non-Specific Urethritis with "Leukomycin" (Chloramphenicol) (Die lokale Behandlung der unspezifischen Urethritis mit Leukomycin) SIKORSKI, H (1954) *Z Haut- u GeschlKr*, **17**, 145

Complement-Fixation Test for Enzootic Abortion in Ewes in Non-Specific Urethritis with a Comparison of the Complement-Fixation Test for *Lymphogranuloma* Venereum WILLCOX, R R, and STAMP, J T (1954) *Amer J Syph*, **38**, 459 2 refs

Topical Neomycin in the Treatment of Non-Specific Urethritis Preliminary Report FERGUSON, C, and CARRON, J (1954) *Milit Surg*, **115**, 176

Morphological and Biochemical Investigations of Human Pleuropneumonia-like Organisms (Micromyces) FREUNDT, E A (1954) *Acta path microbiol scand*, **34**, fasc 2, 127 3 figs, 19 refs

Selective Localization of Murine Pleuropneumonia-like Organisms in the Female Genital Tract on Intraperitoneal Injection in Mice NELSON, J B (1954) *J exp Med*, **100**, 311 1 fig, 10 refs

Special Type of Reiter's Disease (Eine besonderer Verlaufsform des Morbus Reiter) KUSKE, H (1953) *Dermatologica (Basel)*, **106**, 157 1 fig

Complete Reiter's Syndrome (Syndrome de Reiter complet) SYLVESTER, L (1953) *Union med, Canada*, **82**, 928

Reiter's Syndrome (Le syndrome de Reiter) FOREST, A (1954) *Rev Rhum*, **21**, 517 Bibl

Arthritis associated with Non-Gonococcal Urethritis HARKNESS, A H (1954) *Rheumatism*, **10**, 91 5 figs, 8 refs

Non-Gonococcal Urethritis in the Male PARRINO, P S (1954) *U S armed Forces med J*, **5**, 1249 12 refs

CHEMOTHERAPY

Time-Dosage Relationship in the Treatment of Treponemal Diseases with a New Combination of Three Penicillin Salts Laboratory and Clinical Basis for Effective Therapy REIN, C R, BUCKWALTER, F H, MANN, C H, LANDY, S E, and FLAX, S (1954) *Amer J Syph*, **38**, 408 12 refs

A combination of three salts of penicillin is advocated by the authors for the treatment of treponemal diseases Each dose of 2 ml contains in aqueous suspension 300,000 units potassium benzylpenicillin, 300,000 units N N′-dibenzylethylenediamine di(benzylpenicillin) Higher and more prolonged blood levels were obtained with a single injection of 2 ml than with a single injection of 4 ml procaine penicillin in oil with 2 per cent aluminium monostearate (PAM), although both contain 1,200,000 units of penicillin Initial trials in syphilis, yaws, and pinta are reported as giving highly encouraging results [but no clinical details are given] It is suggested that this type of penicillin preparation is suitable for use in those countries where patients must be treated with a single injection *V E Lloyd*

Oral Chloramphenicol Therapy in Venereology (Perorale Chloramphenicol-Behandlung in der Venerologie) DAESCHLEIN, G (1954) *Z Haut- u GeschlKr*, **17**, 141, 9 refs

Toxic Reactions in Antibiotic Therapy CHEYMOL, J (1955) *Pharm J*, **174**, 74

PUBLIC HEALTH AND SOCIAL ASPECTS

Decline and Fall of Syphilis in New York State, 1936–1953 II Early Congenital Syphilis VOUGHT, R L, MELLO, L DE, and AMES, W R (1954) *Amer J Syph*, **38**, 361 1 fig, 3 refs

The annual attack rate for early congenital syphilis (that is, syphilis in infants of less than 1 year) in New York State has been reduced by approximately 98 per cent since the inauguration of a syphilis control programme in 1936 and, since 1950, has become steady at about seven cases per 100,000 live births The effectiveness of the control measures is indicated by this steady decline in the incidence of early congenital syphilis in spite of an increase in the annual attack rate for early acquired syphilis between 1943 and 1951 These measures include the obligatory reporting of cases of syphilis to the public health authorities, provision of a free serological diagnostic service to physicians, obligatory treatment of all infectious cases and infected contacts, obligatory prenatal and premarital serological tests free

supply of penicillin for the treatment of syphilis, and education of the population and physicians During the same period the prevalence of syphilis among parents decreased by 58 per cent although it remains high (1 3 per cent)

It is inferred that syphilis transmission in the State has now reached a steady level, but since this level is relatively high there is no assurance that severe outbreaks will not occur in the future, particularly if population movement is increased or control measures are lessened

V E Lloyd

Venereal Diseases in Children KANDHARI, K C (1954) *Punjab med J*, **4**, 68

Social Factors affecting the Incidence of Syphilitic Psychosis a Research Note FRUMKIN, R M, and BAKER, S R (1954) *Ohio St med J*, **50**, 1042 1 ref

Venereal Disease Contacts of Merchant Seamen STUART, J, and JOYCE, G (1954) *Publ Hlth Rep (Wash)*, **69**, 1197 1 fig

Venereal Foci in Ports WILLCOX, R R (1954) *J roy nav med Serv*, **40**, 187 13 refs

Venereal Disease in Agricultural Migrants—New Jersey, 1953 SHEPARD, A C, and PAGE, W J (1954) *Publ Hlth Rep (Wash)*, **69**, 831 2 refs

Gonorrhea Control Measures A Study in New Hanover County, N C LEE, S S (1954) *Publ Hlth Rep (Wash)*, **69**, 998 2 figs, 23 refs

Prenatal Care in New York City, 1951 BAUMGARTNER, L, GOLD, E M, JACOBZINER, H, WALLACE, H M, WEINER, L, SCHMIDT, W M, and WORCESTER, J (1954) *Publ Hlth Rep (Wash)*, **69**, 937 4 refs

Long-term Trend and Economic Factors of Paresis in the United States DONOHUE, J F, and REMEIN, Q R (1954) *Publ Hlth Rep (Wash)*, **69**, 758 2 figs, 10 refs

Comments on the New Law for the Control of Venereal Diseases (Bemerkungen zum neuen Gesetz zur Bekämfung der Geschlechtskrankheiten vom 23 Juli 1953) KEILIG, W (1954) *Hautarzt*, **5**, 410 8 refs

Environmental Factors in the Tuskegee Study of Untreated Syphilis OLANSKY, S, SIMPSON L, and SCHUMAN S H (1954) *Publ Hlth Rep (Wash)* **69**, 691 13 refs

MISCELLANEOUS

Study of Ducrey s Bacillus and Recognition of a Gram-Positive Smooth Phase DEACON, W E, ALBRITTON, D C, EDMUNDSON, W F, and OLANSKY, S (1954) *Proc Soc exp Biol (N Y)*, **86**, 261

Stock cultures of Ducrey s bacillus have been cultivated at the Venereal Disease Research Laboratory, Chamblee, Georgia, on infusion agar slopes overlaid with sterile defibrinated rabbit's blood and on Eugon Agar (BBL) plates with 15 per cent rabbit s blood incubated anaerobically and also in a partial atmosphere of CO_2 Small colonies of long chained Gram negative streptobacilli appeared after 72 hrs at 35° C The colonies were 0 5 to 1 0 mm in diameter and had a rough surface texture

When pus from three chancroidal buboes was cultured on the same media, white dewdrop colonies 1 to 3 mm in diameter with a surrounding zone of haemolysis were obtained on the solid medium Microscopical examination showed slender Gram *positive* rods with little, if any, tendency to chain formation, the average field showing only a few diplobacilli On subculture, they rapidly reverted to the classical Gram-negative forms seen in the stock cultures, but could be maintained in the Gram-positive form by frequent subculture under anaerobic conditions Intradermal inoculation into rabbits produced subcutaneous abscesses in which the Gram positive rods could be demonstrated, although attempts at recovery the day after rupture of the abscesses were unsuccessful No lesions were produced by inoculation of the old stock strains

The authors conclude that previous descriptions of Ducrey s bacillus have dealt with a rough, non pathogenic variant and that the smooth form of the organism has not previously been recognized

A E Wilkinson

Chemotherapy of Chancroid Clinical Observations in 87 Cases MENDELL, H E, FOXWORTHY D L and WORNAS, C G (1954) *Amer J Syph*, **38**, 483 6 refs

A comparative study of the therapeutic efficacy of sulphadiazine, streptomycin chlortetracycline (aureomycin), and oxytetracycline (terramycin ®) was made in the treatment of 87 cases of chancroid occurring in U S Air Force personnel on Okinawa In 72 per cent of the cases the Ducrey bacillus was isolated All cases were followed up for 2 months after completion of therapy The authors point out that the diagnosis of chancroid must be made cautiously in view of the many non chancroidal lesions involving the penis In their view the specificity of smear examination and skin tests leaves much to be desired and they have found the clinical characteristics of the lesion and the response to conservative therapy with potassium permanganate far

more reliable The following treatment schedules were employed

(1) streptomycin, 1 g intramuscularly daily for 7 days (22 cases),

(2) sulphadiazine, 1 g four times a day for 7 days (thirteen cases),

(3) streptomycin, as above for 5 days, followed by sulphadiazine for a further 5 days (twelve cases),

(4) aureomycin, 250 mg four times a day for 4 days (twenty cases),

(5) oxytetracycline, 250 mg four times a day for 4 days (twenty cases)

Results showed that all four substances were equally effective in the chemotherapy of chancroid in the dosages indicated Sulphadiazine and streptomycin in combination appeared to exert some synergistic effect and shortened the healing period of the ulcers Since neither of these drugs has any effect on *Treponema pallidum* they are to be preferred when a syphilitic infection has not been ruled out, in order not to mask the presence of syphilis *Neville Mascall*

Cat-Scratch Disease Report of 160 Cases DANIELS, W B, and MACMURRAY, F G (1954) *J Amer med Ass*, **154**, 1247 2 figs, 15 refs

The authors have analysed 160 cases of cat-scratch disease, 27 of which they saw personally The majority of the patients were young, over one-third being under the age of 10 years In twelve instances there were household epidemics involving 26 victims, mostly children

In 148 of the cases a history of contact with cats was obtained of these 148 patients 93 had been scratched by the cat, but in a further 38 cases no such history could be obtained The primary lesion, usually a scratch or papule persisted for several weeks, and the duration from the initial scratch to the development of the primary lesion was 3 to 14 days Within a further 7 days enlargement of lymph nodes was observed, which might subside in 2 weeks or still be present 2 years or more afterwards Suppurative lymphadenitis occurred in 47 patients Constitutional symptoms, present in 80 per cent of the patients were those associated with a general infection, including fever, chill, headache, anorexia, and malaise Evanescent rashes were noted in eleven patients, and two others developed an eruption of erythema nodosum type on the legs In all the patients there was a positive reaction to an intradermal test with cat-scratch disease antigen

The more unusual forms of the disease are discussed with reference to individual cases Treatment is briefly mentioned, the authors believe that the newer antibiotics may be helpful, but their usefulness is difficult to assess because the disease is self-limiting

T Anderson

Treatment of Chancroid Infection A Report of 25 Cases PAPARELLA, J A (1954) *Amer J Syph*, **38**, 345 2 figs, 3 refs

The results of chemotherapy in 25 proved cases of chancroid infection are reported In all the cases smears were cultured, *Haemophilus ducreyi* being isolated in seventeen instances Bubo formation was seen in eleven cases, including five in which culture was negative None of the patients developed syphilis

Aureomycin alone was given to 72 of the patients, a combination of aureomycin and sulphadiazine to five, streptomycin and sulphadiazine to five, aureomycin and streptomycin to two, and streptomycin alone to one The dosage of aureomycin was 1 g initially and 250 to 500 mg every 6 hrs for 3 to 5 days

Satisfactory results were obtained with aureomycin alone, no added benefit being observed when aureomycin in combination with other antibiotics or with sulphadiazine was given Ulcers healed in 4 to 7 days after the start of treatment, adenopathy disappearing after a somewhat longer period

The author admits that aureomycin may mask the early signs of syphilis or lengthen the incubation period, and suggests that serological tests for syphilis should be carried out for 3 to 5 months after treatment with aureomycin ceases [This is an easy matter in military practice, but is a considerable drawback to the use of aureomycin in civilian practice or where supervision for 3 to 5 months is not possible] *Robert Lees*

Treponematosis Control Program of the World Health Organization The Treatment of Yaws with Benzathine Penicillin G GRIN, E I, GUTHE, T, PAYANANDHA, LA-ONG, D'MELLO, J M F, and SWAROOP, A S (1954) *Amer J Syph*, **38**, 397 2 figs, 26 refs

Advantages and Dangers of Local Oral and Intravaginal Penicillin Therapy (Vorzuge und Gefahren der lokalen oralen und intravaginalen Penicillintherapie) GRASREINER, W (1954) *Derm Wschr*, **130**, 749 3 figs, 23 refs

Critical Remarks on the Use of Penicillin in Prophylaxis against Blennorrhoea in the Newborn (Kritisches zur Penicillin-Blennorrhoeprophylaxe der Neugeborenen) SCHULTZE, K W, and HARTMANN, A (1954) *Dtsch med Wschr*, **79**, 1631 13 refs

Multiple Lymphogranulomatosis Venereum of the Jejunum (Lymphogranulomatose veneriennne multiple de jejunum) DA COSTA BRUNO (1954) *Arch Mal Appar dig*, **43**, 686 10 figs, 37 refs

Comparative Study of the Bacterial Flora of the Conjunctiva in the Newborn and of the Cervix Uteri of the Mother, with an Investigation of the Actions of Silver Nitrate and of Penicillin on the Conjunctival Flora (Estudio comparativo de la flora bacteriana de las conjunctivas de recien nacidos y de la del cuello uterino de sus madres, y de la accion del nitrato de plata y de la penicilina respectivamente sobre la flora conjuntival del recien nacido) BARRERE, L E (1954) *An Fac Med Lima*, **37**, 62

Epidemiology, Aetiology and Prophylaxis of Lymphogranuloma Inguinale [In English] FAVRE, M, and HELLERSTROM, S (1954) *Acta derm-venereol (Stockh)*, **34**, 1 19 figs, bibl

Possibility of Eradication of Congenital Syphilis (Es posible erradicar la sifilis congenita) GIFFORD, A J, WRIGHT, J J, SHEPS, C G, and TAYLOR, E E (1954) *Bol Ofic sanit pan amer*, **37**, 193 2 refs

Pre-Columbian Ceramic Vases of the Ancient Nazca Culture, showing possible Gummata of the Leg WEISS P, and GOLDMAN, L (1954) *Amer J Syph*, **38**, 145 1 fig, 6 refs

History of the Spread of Syphilis in Africa from Contemporary Travellers' Records (Die Geschichte der Verbreitung der Syphilis in Afrika nach zeitgenossischen Reiseberichten) SPRINGER, A (1954) *Hautarzt*, **5**, 227 Bibl

Brit J venet Dis (1955), **31**, 65

NEISSER AND NEISSERIAN PRINCIPLES IN VENEREOLOGY*†

BY

L W HARRISON

London

I value very highly the honour of having been invited to give the opening address at this centenary celebration of Neisser's birth, but I am very acutely conscious of my defects as an historian and hope that members of the distinguished company here to-night will fill the gaps that are inevitable in my story, because only with your help will the Osler Club honour worthily the memory of a man who used his outstanding abilities in the service of mankind to such a degree and with such success as to entitle him to high prominence in every history of medicine, indeed in every history of social endeavour

My brief stipulates not much biography and restricts me, by my own wish I may say, to only one of the fields in which our hero shone, but in this field I may wander a little from the strictly Neisserian path to comment on contemporary events in venereology which may not perhaps be now familiar to you, but have always seemed to me to be interesting and instructive

For a number of the facts in my condensed biography I am indebted to Neisser's "Beitrage, zur Pathologie und Therapie der Syphilis" (Neisser, 1911a), and to the obituary which appeared in the *Lancet* (1916) Neisser's birthday was on January 22, 1855, which I calculate fell on a Monday, whatever that may have portended He was the son of a physician, an advantage in respect of family atmosphere which, from personal experience, I have always thought very valuable to a member of our profession

He became M D at the age of 22, his thesis being a monograph on diseases due to *T echinococcus*, thus disclosing early his taste for precision in instruments of diagnosis, microscopy in particular

He quickly became assistant to Oskar Simon, the Director of the Department of Dermatology in the University of Breslau, and in 1879, 2 years after qualification, at the age of 24, he announced in a preliminary communication (Neisser, 1879), that he had seen in gonorrhoeal pus certain cocci of distinctive appearance which he regarded as the cause of the disease Thus the gonococcus was presented to the world, and Neisser s priority in its discovery is universally recognized in the fact that today the proper name of the gonococcus is *Neisseria gonorrhoeae*, and micro-organisms having similar morphological characteristics are Neisseriaceae

Five years after qualification, in spite of the fact that one does not usually become entitled to such a position until one has become much more decayed than one expects to be at the age of 27, he succeeded Oskar Simon and became Professor Extraordinary and Director of the Department of Dermatology The events justified such an apparently courageous selection because Neisser proved to be no disciple of the learned Dr Pangloss, who, you know, believed that everything was for the best in the best of all worlds On the contrary, he showed himself to be a born reformer and a "live wire" in his ability to get things done, for example, by 1892 he had got the hitherto primitive Allerheiligen Hospital brought thoroughly up to date

In 1899 and 1902, together with the foremost workers in the field of venereology, he attended the historical international conferences in Brussels at which great men now revered in the world of social endeavour, impressed by the evil effects of venereal diseases, sought to convince the world that something ought to be done about them and enunciated principles of combating these diseases which largely hold good to-day

At the conference in 1899, Neisser made a powerful plea for greater attention to be given to gonorrhoea, a translation of his paper, published in *Medical News* (1900), was entitled "Gonorrhoea, its Dangers to Society" It ended

> 'The first step in reform is for the public to know and to appreciate the dangers and the significance of venereal diseases More effectual than all legal or police regulations will be the individual protection afforded by our present knowledge in this matter, if physicians and the laity will but realize our modern advances in this subject I have not the slightest doubt that the present danger which

* Received for publication January 28 1955

† Read before the Osler Club to celebrate the centenary of the birth of Albert Neisser on January 22 1855 (with some additions)

threatens the human race from gonorrhoea will be greatly lessened and the spread of the disease distinctly limited as the result of the discussion here"

In 1902, Neisser founded the German Society for combating Venereal Disease, 12 years before the corresponding body, The National Council for combating Venereal Diseases, was formed in Great Britain

In August, 1903, stimulated by the work of Metchnikoff and Roux on experimental syphilis in monkeys and doubtless by similar researches in Vienna and St Petersburg, Neisser began his own studies in Breslau He soon found a number of practical disadvantages of conducting a research on monkeys in Europe The chief were the cost of the animals and the uncertainty of their life in the European climate as against the chronicity of syphilis So he planned an expedition to the tropics, where the monkeys he wanted to use were plentiful and in natural surroundings, and he and Dr Baermann finally set out for Java in the middle of January, 1905, accompanied by their wives In May, 1905, they were joined by Dr Halberstaedter in Batavia, where the research had been set up According to Neisser's "Beitrage" (Neisser, 1911a) he might have carried out his work in Singapore or thereabouts, but the English authorities did not favour this project He returned to Breslau in October, 1905, but retained control of the Java work by weekly letters and a further visit in November, 1906, continuing the work there until 1907 Altogether his experimental work on syphilis in Batavia and Breslau lasted from 1903 to 1909 I am not sure how the research was financed in 1905, but think it must have been from his own pocket because in the "Beitrage" already mentioned he was careful to acknowledge outside assistance from 1906 inclusive onwards His letter to the Reichs Chancellor asking for Government support should be read by anyone wanting to wring money out of a cold-blooded Treasury for special work in venereology, it ran to about 7,000 words and amongst the arguments for support was, besides the plea that the work would be to the nation's honour, the hope that the research would result in the discovery of a prophylactic vaccine against contraction of syphilis and also perhaps as a therapeutic anti-serum, I will revert to that later Neisser also received assistance from a private benefactor and from two German shipping lines, the Hamburg-Amerika and the Norddeutscher Lloyd The Government grants for his experimental work amounted to 230,000 marks

His experimental work and that of his colleagues from 1903 to 1909 is fully described in the "Beitrage" * I was interested to note in some of the illustrations, for example, No 19 on p 23 and No 8 on p 13, that the workers handling these syphilitic monkeys wore no gloves It amused me very much because I never wore gloves at the Rochester Row Hospital from 1909 to 1914, and was often told what a fool I was for running such risks

Neisser's experimental work added very greatly to existing knowledge on the behaviour of syphilis in the body and on the body's reaction to the parasite As one result of it, he became frankly sceptical of any success resulting from efforts to immunize against syphilis or of producing a therapeutic anti-serum His views on the prospects of obtaining a prophylactic vaccine were shared by Metchnikoff but this will o' the wisp has lately attracted some leaders in syphilology They ought to read Neisser's and Metchnikoff and Roux's articles on experimental syphilis History has its uses ! One strong objection to vaccination against syphilis, which was voiced I think by Metchnikoff, is that a vaccine might make the body anergic to attack by the spirochaete so that, although infested and swarming with these germs, it would not respond with a surface lesion, just as mice and a certain proportion of rabbits do not respond though their bodies are swarming with the germ

During Neisser's absence in Java, the causal organism of syphilis, which the pundits now say we must call *Treponema pallidum*, was discovered by Fritz Schaudinn On the Schaudinn-Hoffmann combination † and its origin I hope to have time to speak a little later

Ehrlich's dramatic reaction to the news of Schaudinn's discovery has been graphically described in Fraulein Marquardt's biography of Ehrlich (Marquardt, 1949), which ought to be read by everyone interested in medical history His delight over it was just a little tempered by regret that the honour of it had not fallen to his great friend, Neisser The incident testifies to the respect and friendship which the great Ehrlich felt for his friend Albertus Magnus, as he called him and also to the bigness of Ehrlich, who saw in the discovery of the micro-organism of syphilis a bright prospect for the forging of antisyphilitic weapons

In Java, Neisser's team, notably Baermann, quickly confirmed Schaudinn's discovery and his experimental work led to his association with Wassermann and Bruck in the application of the Bordet-Gengou phenomenon of complement fixation ‡ to the diagnosis of syphilis For what better

* A copy brought by Dr Worms was on show at the meeting
† Schaudinn and Hoffmann (1905a b c)
‡ Bordet and Gengou (1901)

negative control in such a test could one have than a monkey which had not been inoculated with syphilis, and what better positive control than one which, having been negative had been inoculated some weeks previously and had responded to the inoculation? Also the glands, bone marrow, etc., of such an inoculated animal could be a convenient source of antigen in such a test We know now that the antigen made of such tissues was not purely spirochaetal, as Wassermann and Bruck quite naturally imagined, but Neisser's monkeys must have seemed to Wassermann and Bruck heaven-sent material for their experiments in complement fixation for the diagnosis of syphilis *

In 1907, the 25th anniversary of Neisser's professorship was marked, *inter alia*, by the publication of two volumes of the *Archiv fur Dermatologie und Syphilis* (*Wien*), Nos 84 and 85 entitled *Festschrift Neisser*, to which over sixty of his pupils contributed original articles They and the laudatory dedication written by Harttung, Jadassohn, and Schaffer (1907) testify to the affection and respect in which Albert Neisser was held by these many workers, themselves mostly notable figures in the world of dermatology and syphilology An even greater tribute was paid in 1916 as I will mention later In 1907 also he was made Professor-in-Ordinary

After the discovery of "606", Neisser quickly became convinced that generally this great new remedy required the assistance of mercury, and he is thus in my mind not only the Father of the Gonococcus, as he was often called, but also one of the fathers, and a very influential one at that, of what is now often called the synergistic treatment of syphilis I hope to speak at greater length on this subject a little later, but may say here that his views on it may conveniently be read by English-speaking students in the text of his Cavendish lecture delivered before the West London Medico-Chirurgical Society on June 27, 1911, and published in the *West London Medical Journal* (Neisser, 1911b) That lecture also discloses the high quality of Neisser's reasoning and the wisdom of his views After it he received from the President of the West London Medico-Chirurgical Society, Dr Phineas Abraham, the first Phineas Abraham gold medal of the Society given every 3 years for work of outstanding merit in medicine

Neisser died on July 31, 1916 For a number of years he had suffered from diabetes and renal calculus, but in spite of these crippling handicaps he retained a lively interest in his work almost to the very end Although he had renal colic with cystitis he insisted on attending an exhibition in Brussels in the month he died On his return home he set out to attend a meeting in Dusseldorf but was forced to retire to Berlin for an operation for stone in the bladder Two days later he returned to his beloved Breslau, but sepsis and high fever developed and on July 31, as stated, he died in coma

In the *Archiv fur Dermatologie und Syphilis* (1916) 55 pages were devoted to tributes to Neisser's great qualities, and besides the 53-page account of his achievements by Jadassohn (1916), who succeeded him, was signed testimony to the affection and respect in which he had been held by over 140 of his old pupils now holding more or less important positions in different parts of the world

Before I discuss in more detail work in venereology with which Neisser was more or less closely associated, I feel I cannot do better than quote the beginning of the obituary in the *Lancet* (1916), published, it should be remembered, at a time when rivers of hate were flowing between this country and Germany Despite this, the *Lancet* said,

"By the death of Albert Neisser on July 30,* Germany lost one of her greatest scientists and the whole world is poorer for the loss"

According to the *British Medical Journal* (1917) he left his villa to the city of Breslau to be maintained as a museum for contemporary works of art and the rooms to be used for high-class concerts

I should like now to speak at greater length about Neisserian principles in venereology and, whilst I do so, perhaps I may be pardoned if in passing I digress here and there to enlarge a little on discoveries in venereology which were made in Neisser's time

In my mind Neisser's contributions to venereology which stand out most forcibly, apart from his very valuable work on experimental syphilis, are

(1) His insistence on the control of the treatment of gonorrhoea under guidance by microscopical examination of discharge

(2) His stand against the indiscriminate use of astringents in the treatment of gonorrhoea

(3) His very early insistence on the concurrent use of mercury, preferably in the form of insoluble suspensions with arsphenamine remedies in the treatment of syphilis

Insistence on microscopic tests debunked a host of claims to cure gonorrhoea in double-quick time which were made by many authors who disdained or were ignorant of such a method of control and were still going strong in this and other countries until some years after I became employed in venereology Since I undertook the delivery of

* Wassermann Neisser and Bruck (1906)

*The date given in the *Arch Derm Syph* (*Wien*) was July 31

this address, I have been interested to study the methods of treating gonorrhoea which were being practised in this and various other countries from the time of discovery of the gonococcus and afterwards right up to the war of 1914–18 and later, and I have been astonished at the claims made for them, claims which could not possibly have been supported by proper tests of cure such as were insisted upon by Neisser and are practised in all good research centres to-day

I must not spend too much time on this subject, but may say that some of the treatments would make the modern venereologist's hair stand on end For example, the late Sir Watson Cheyne in an article on the abortive treatment of gonorrhoea (Cheyne, 1882) mentioned a method used by Debeney in which a solution of silver nitrate, 64 grains to the ounce, was injected into the urethra Apparently Ricord used a strength of 16 grains to the ounce, but by about 1882 a more popular line was an injection even so dilute, Watson Cheyne said, as 1 in 3,000 Cheyne at that time favoured a medicated bougie of eucalyptus oil and iodoform and at one time, following the advice of Robert Koch, incorporated in the bougie, presumably of 15 grains, one-sixteenth of a grain of mercury perchloride, which would give a strength of 1 in 240 perchloride He does not seem to have remained favourably impressed by the results of these forms of treatment One author claimed to cure the disease in an average of 6 days by injecting sulphurous acid in a dilution of 1 in 16 In 1883, Curtis, an American author, after criticizing existing methods of treatment, none of which, he said, seemed able to cure gonorrhoea in less than 3 weeks, recommended douching the whole urethra through a back-flow catheter with as much as 10 quarts of water as hot as the patient could stand, following this with a solution of tannic acid, 16 grains to the ounce in a suspension of iodoform, also 16 grains to the ounce By this method he claimed cure in an average of 1 week I once saw a patient who had been treated by a hot douche method, which seems to have been rather popular at one time, his urethra was in a horrid mess F P Atkinson (1886) mentioned great improvements in the treatment of gonorrhoea and then described his own method If the discharge was not lessened by internal treatment, the patient was to have urethral injections of zinc sulphate, 3 grains to the ounce, or of potassium permanganate, 1 in 480, or of silver nitrate 2 to 5 grains to the ounce

The late Sir Jonathan Hutchinson (1892) seems also to have favoured astringents, recommending zinc chloride, 2 grains to the ounce

As evidence also of the fact that quicker cures were claimed than was possible when cures were judged by microscopical examination of secretions may be quoted some periods of stay in Army hospitals mentioned by Neisser in his address to the first Brussels Conference, already mentioned They were Germany, 29 to 31 days, Austria, 36 to 37 days, Belgium, 27 to 34 days, France, 26 to 34 days

Some may say that was in the 1890s or earlier and that people have since learnt better, but I can say that after I had taken over the treatment of gonorrhoea at the Rochester Row Hospital and also during the war of 1914–18 3-week cures were quoted to me *ad nauseam* by my senior officers

As against such claims I may quote an article by Paul Neisser in the Festschrift number of the *Archiv fur Dermatologie und Syphilis* (1907) already mentioned Controlling results by microscopical tests, he compared five methods of treatment, four with different compounds of silver and one by purely medicinal and dietetic measures The durations were 49 to 53 days by the different silver preparations and 85 5 days by purely medicinal and dietetic treatment The author concluded that the scientific treatment of gonorrhoea without the use of a microscope was impossible, and I would say the same to-day

I can quote one example of the truth of this dictum, against myself In the war of 1914–18, when for my sins I commanded a large military V D hospital in France, I read an article in an American medical periodical in which the author claimed to cure gonorrhoea in about 10 days by giving the patient an intramuscular injection of 100 mg mercury succinimide every other day for some days That seemed to accord with our experience that in patients suffering from both syphilis and gonorrhoea the discharge cleared up more quickly than in those with only gonorrhoea, we had thought it was the "606" which was doing it but events proved that it was the mercury I obtained some succinimide of mercury and tried it on the cases of simple gonorrhoea without syphilis the effect seemed to be marvellous The discharge seemed to clear up wonderfully and, to my shame be it said, I approved the discharge from hospital of a large number of patients in less than 14 days after admission They had answered the usual Army tests of cure, as far I could see, and in existing circumstances it certainly was impracticable to apply microscopic tests, we simply had not the staff for it But later when I examined a slight gleet in some of the cases I found the scanty pus cells just swarming with gonococci

The lesson shows how right was Albert Neisser and his pupil and namesake in insisting on microscopical control of gonorrhoea I think that venereologists who have followed such principles, and I like to think they comprise the majority of those engaged in this work under the National V D Scheme since 1920, must have prevented a very great amount of transmission of this disease to innocent persons

In this microscopic control, I should think that Neisser himself and many other authors must have misdiagnosed as gonococci many very similar cocci in discharges which they examined before Gabriel Roux, in 1886, pointed out that gonococci are decolorized by the Gram method of staining

On the question of the use of astringents in the treatment of gonorrhoea of which Neisser was a foremost opponent, he being an advocate of bactericidal methods and particularly of protargol and other organic preparations of silver, I have been interested to try to discover how long astringent methods prevailed in this country, and now I think I am entering on controversial ground Nevertheless, some of the following facts which I have collected may possibly interest you

In 1912, being convinced that the problem of syphilis was solved, requiring only the discovery of the optimum amount of Salvarsan and mercury to be administered, but feeling that much more work ought to be done on gonorrhoea than was then thought necessary, I asked for charge of the gonorrhoea ward at the Rochester Row Hospital and for an assistant to help me there and in the laboratory I felt that any investigation should be made in close collaboration with the laboratory, and that the simplest way of achieving this would be to have charge of both departments

At that time the routine method of treatment was according to the teaching of Janet (1892), by irrigation with potassium permanganate of a strength ranging from 1 in 4,000 to 1 in 2,000 I am not sure what was the prevalent treatment elsewhere but believe that, if any local treatment at all was used, it was on Janet lines, or by silver preparations, or by frank astringents such as lead acetate or zinc sulphate I soon concluded that solutions of 1 in 4,000 potassium permanganate and stronger were definitely astringent, and I reduced the strength to 1 in 8,000 because, like Neisser, I did not believe that astringent treatment was scientific Thereafter I discouraged the use of permanganate of greater strength than 1 in 8,000, and I believe that my views on this point prevailed throughout the Army during the 1914–18 war, and certainly in the V D treatment centres throughout Great Britain from 1920 onwards There is some evidence that in civilian circles during the 1914–18 war greater, more astringent strengths of permanganate were used because one eminent urologist poured scorn on the strengths used in the Army, saying in effect "If you're going to use permanganate, use it, don't fiddle about with solutions weaker than 1 in 2,000" I was rather disturbed by this criticism, and discussed the question with the late Mr Wyndham Powell, who, I believe, knew more about the inside of the male urethra than most people, and he said that such concentrations as 1 in 2,000 were all right so long as one dealt with the resulting infiltrates after the discharge had almost dried up That, from such an authority, was sufficient to encourage me to continue with my "fiddling" low concentrations, which were non-astringent, though, as I believed, detoxicant I am encouraged in my view that permanganate as used in the Janet manner was astringent by its taste and its classification amongst the astringents by Perutz (1934)

So, at the possible risk of having my toes trodden upon this evening, I have dared to class the treatments prevailing in civilian circles in Great Britain before the National V D Scheme was on its feet as more liable than later methods to be followed by stricture of the male urethra So far as other people of British nationality are concerned, I think that most of the 200,000 British soldiers treated for gonorrhoea during the 1914–18 war escaped that risk, though the tests of cure mostly violated Neisserian principles in dispensing with microscopical examination

It was natural that I should seek statistics which would decide whether, by the milder, non-astringent, non-irritant method prevalent throughout Great Britain from at any rate the early 1920s, stricture of the male urethra has been greatly reduced I think anyone who has to deal with the male urethra, whether as venereologist or as urologist, will agree that stricture of the urethra has now been relatively rare for a number of years, the stricture parades of the old days are no more, and some even say that the passage of a curved sound is becoming a lost art But those are possibly only impressions I wanted to find something more concrete and, not having time to search through the records of many hospitals, I thought that possibly the Registrar-General's Tables showing the deaths from stricture might give some information I think, however, that despite the old tag that one can prove anything with statistics, this is an instance where the figures do not prove the case As, however, they are interesting, I am venturing to show what I have collected, in two Tables Starting on the assumption that most

strictures of the urethra are due to urethritis, most commonly gonorrhoeal, or to its treatment, or to both, I aimed first to discover how long after contraction of gonorrhoea the stricture killed its man, and Table I seems to give the answer The peak decade for contraction of gonorrhoea is from 20 to 29 years and, as the figures in this Table show, the peak decade for deaths from stricture is from 60 to 69, or 40 years later You will notice in the Table that there was a significant fall in the deaths from stricture in the decade 1941 to 1950 Going into the matter more closely, I aimed to see just about when the deaths began quite definitely to decline and collected the figures shown in Table II As you will see, the figures are in four main periods, from 1912 to 1920, from 1921 to 1936, from 1937 to 1943, and from 1944 to 1953

TABLE I

DEATHS FROM URETHRAL STRICTURE IN MALES (1921–50) BY AGE GROUPS AND DECADES

Age Groups (yrs)	Decades		
	1921–30	1931–40	1941–50
All Ages	3 484	3 384	2 116
0–19	5	3	3
20–29	30	21	5
30–39	113	71	32
40–49	468	288	130
50–59	917	793	352
60–69	1 165	1 259	704
70–79	662	775	700
80 and over	124	174	180

In the first, with an average of 404 deaths from all urethral diseases per annum, separate figures for stricture were not obtainable, but those in the fourth and fifth columns of the periods 1921 to 1943, which were included in those in the second and third columns, show clearly that most of the 404 in the first period must have been due to stricture

The fourth period shows the most significant decline and this in spite of the increase in gonorrhoea which must have occurred in the civilian population in the 1914–18 war, when 200,000 British and Dominion soldiers were treated for this disease

But before I could confidently say that the great decline during the period 1944 to 1953 was due to the better treatment of gonorrhoea from a time 30 to 40 years before 1944, I had to remember the sulphonamides and the antibiotics and possibly improvements in surgical technique which might have made the treatment of urethral stricture safer However, the figures do show that in the past dozen years or so, deaths from stricture of the male urethra have become about a quarter of what they were in the period 1921 to 1936, and still less than in the period before 1921

As for gonorrhoea in the female, the prevailing treatment when I first had to take an interest in this branch, in the early 1920s, seemed to me even more horrifying than those I have sketched on the male side, and I have often wondered how much of the sterility attributed to gonorrhoea in the past was due to the strictured cervices following the terrible strengths of silver nitrate which used to be applied there

I come now to the last portion of my essay, namely Neisser s connexion with progress in the management of syphilis, and I should like to digress

TABLE II

DEATHS FROM DISEASES OF THE MALE URETHRA INCLUDING STRICTURE, WITH DEATH RATES PER MILLION

Period (yrs)	All Urethral Diseases including Stricture		Stricture only		Factors			
	Average per annum	Death rates	Average per annum	Death rates	Maltreatment 30–40 yrs before	Treatment of Stricture: Sulphonamide Guards	Treatment of Stricture: Antibiotic Guards	Treatment of Stricture: Surgical Improvements
1912–20	404	21–31	Not shown separately in Registrar General s Tables		Yes	No	No	?
1921–36	389	18–24	355	16–23	Yes	No	No	?
1937	357	18	346	18	Yes	Yes	No	?
1938	346	17	323	16	Yes	Yes	No	?
1939	326	17	304	15	Yes	Yes	No	?
1940	301	16	277	13	?	Yes	No	?
1941	327	19	300	17	?	Yes	No	?
1942	319	19	293	17	?	Yes	No	?
1943	288	18	255	16	?	Yes	No	?
1944			226	14	?	Yes	Yes	?
1945			195	12	No	Yes	Yes	?
1946			188	10	No	Yes	Yes	?
1947			187	10	No	Yes	Yes	?
1948	Not extracted		170	8	No	Yes	Yes	?
1949			161	8	No	Yes	Yes	?
1950			131	6	No	Yes	Yes	?
1951			117	6	No	Yes	Yes	?
1952			114	5	No	Yes	Yes	
1953			93	4				

a little by talking about the discovery of *T pallidum* For this I am indebted largely to the story related by Metchnikoff (1908), who reported that at the International Health Congress in 1903, Bordet had told him that he and Gengou had seen in some chancre juice stained with Kuhne's carbol methylene (blue) and afterwards with Nicolle's gentian violet, a large number of very fine spirilla, rolled like a corkscrew, and very faintly stained But neither they nor Metchnikoff and Levaditi had been able to repeat this observation until after Schaudinn's discovery in 1905 Further, Metchnikoff and Levaditi had examined fresh juice to see whether they could detect any movement, but had failed to find anything which might suggest the presence there of some invisible motile micro-organism

The stimulus to the discovery of *T pallidum* arose really from the claim of one Siegel (1906) that a body which he had seen in syphilitic material, and which he called *Cytorycles luis*, caused syphilis This body is illustrated in Metchnikoff's article and was thought by most non-German authorities to be just organic debris, as indeed it later proved to be, but in Berlin, Siegel's claim was pressed so hard that Franz Eilard Schultze, Professor of Zoology, got together a commission of experts to examine the question from all angles Fortunately, Fritz Schaudinn, a first-class protozoologist and microscopist, was chosen to examine specimens, and Erich Hoffmann, a first-class clinician, to say what was syphilitic material and what was non-syphilitic Siegel's claim was quickly disproved and on March 3, 1905, Schaudinn and Hoffmann, by axial illumination, no high-power dark-ground condenser being then available, saw in the juice from an early syphilitic lesion the very fine pale spirillum we now know as *T pallidum* I suggest that anyone who wishes to realize the greatness of Schaudinn's discovery might try examining a fresh specimen of chancre juice with the usual sub-stage—not the dark-ground, of course—condenser and almost closed diaphragm He would start with the advantage of knowing that the organism was there, but I think he could congratulate himself and the maker of his microscope if he saw the pale spirillum

I have mentioned that Neisser after many failures gave little hope of discovering a vaccine as a prophylactic against syphilis, and also his association with Wassermann and Bruck in the application of Bordet and Gengou's phenomenon of complement fixation to the diagnosis of syphilis It seems interesting to me that the Bordet-Gengou phenomenon was to decide a dispute between Bordet and Gengou of Brussels on the one hand and Ehrlich and the Frankfort School on the other as to whether complement was non-specific and able to dissolve and itself be put out of action by either cells or bacteria when these had been sensitized by their appropriate antibodies, or, as Ehrlich and his colleagues contended, there was one complement for cells and another for bacteria The Bordet-Gengou phenomenon proved the unity of complement, and Bordet and Gengou showed that foreign proteins sensitized by their appropriate amboceptors also fixed the common complement Wassermann and Bruck then showed that complement fixation would occur with bacterial extracts, and thus they were able to demonstrate antibody to various diseases including typhoid, cerebrospinal fever, and tuberculosis Thus the way was paved for the demonstration of antibody to the spirochaete of syphilis and inferentially for the diagnosis of this disease by complement fixation Thus another great discovery arose out of a polemic

When I think of the Bordet-Ehrlich dispute on the plurality or the unity of complement and the fact that out of it arose the test commonly known as the Wassermann reaction, *almost the only practical application of complement fixation to diagnosis in clinical medicine*, I cannot help a fantastical likening of it to the fairy story of the magic carpet, Ehrlich and Bordet disputing while Wassermann and Bruck sat on the carpet, eventually flying away with it So I am always glad that the Health Organization of the League of Nations referred to this test as the Bordet-Wassermann Perhaps the WHO might copy their good example

I have already mentioned Neisser's very early insistence on the importance of giving injections of an insoluble preparation of mercury concurrently with injections of Salvarsan It is my belief that, through his great influence in this direction, he prevented a great amount of neurosyphilis of the meningovascular type His views on the subject of using two remedies concurrently are set out shortly in his Cavendish Lecture and more fully in his "Beitrage" on the pathology and treatment of syphilis In this larger work he referred to Ehrlich's views on the plurality of chemo-receptors of micro-organisms so that it seemed reasonable to assail the parasite with more than one poison at a time

Ehrlich's views on this point can be read most conveniently by English-speaking students in his address to the International Medical Congress, London, 1913, which was fully reported in the *British Medical Journal* and *Lancet* (Ehrlich, 1913a, b) In it he said that uncivilized tribes, the more certainly to destroy their enemies, dressed their arrow-tips with more than one poison, and he proposed to dress his amino-benzene arrow with more than one metal

Thus his 1+1 in therapeutic units would equal more than 2 when used concurrently He instructed Karrer to make copper-salvarsan, which proved too toxic, but his successor, Kolle,* found that Karrer's silver and neo-silver Salvarsans were efficacious and were much used at one time

Another preparation which appeared during the 1914–18 war was Luargol, a combination of arsphenamine, silver, and antimony It may be interesting to note that Neisser, in his Cavendish Lecture, mentioned antimony as a possible addition to the chemo-therapeutic armamentarium Luargol thrombosed practically every vein into which it was injected so that towards the end of a course of injections one was searching the skin surface for superficial veins, and that remedy was soon discarded In 1924, Lehnhoff-Wyld, in Paris, having shown that the curative dose of sulpharsenol was lower when there was another metal present in the circulation, produced zinc-sulpharsenol, it proved too painful These views and experiences supporting the general principle that the concurrent use of more than one remedy was more efficacious than the use of one at a time were later well supported on the laboratory side by Clausen, Longley, and Tatum (1942) and on the clinical side by Eagle (1944), but I would now revert to my original contention that Neisser, by his strong advocacy of this principle, has prevented a great amount of neurosyphilis of the meningovascular type Very early in our trials of "606" at Rochester Row, he sent us a German patient for us to continue this combined treatment of his because we had shown that we too believed in it Everybody who had much to do with the early trials of the arsphenamine group of remedies can doubtless cite cases in which "606" alone cured some cases as proved by complete tests many years later, I know of a few in which a single dose achieved that miracle *But those people also know that many patients treated with the arsphenamine remedies alone developed signs of syphilis of the central nervous system*, mostly in the form of cranial nerve palsies There is quite a considerable literature dealing with the subject, the Vienna school in particular contending that these sequelae of the arsenical treatment were due to a neurotropic effect of the remedy, and the Frankfort school contending, as was conclusively proved in the long run, that they were due to a recurrence of syphilis in the affected structures We at Rochester Row were keen Frankfortian partisans and eventually we were very glad that we had early taken the advice of Neisser to give mercury concurrently with the arsenical remedy, especially so because in our own cases treated from 1910 to 1914 we had not a single case of neurosyphilis of the kind mentioned Further, of all the soldiers treated on these lines during the war of 1914–18, I heard of only one case of the kind mentioned in all those treated in the British Army In the early 1920s the Medical Society for the Study of Venereal Diseases organized an inquiry, which was subsidized by the Ministry of Health, to discover whether any such cases had been seen in general clinics or in clinics for diseases of the nervous system after treatment for syphilis in the Army during the then recent war Nicol (1925), who made the inquiry on our behalf, found only one Further, in the cases treated at St Thomas's Hospital from 1920 to 1928, only one had occurred, though our cases included very many that had had very little treatment, the point of importance was that in this treatment the two remedies had been given concurrently In a report on the results of treatment of the St Thomas's Hospital cases, published in 1929 by the Medical Research Council (Harrison, 1929), I contrasted our experience with that of the Syphilis Clinic at the Johns Hopkins Hospital in which, as reported by Moore and Kemp (1926), out of a gross material of 2,500 cases of early syphilis treated with courses of arsphenamine followed by courses of mercury, there had been no fewer than 59* neuro-recurrences manifested by syphilitic meningitis, cranial nerve palsies, and precocious vascular neurosyphilis I believe that the reason was the withholding of mercury at the beginning of treatment whilst doses of arsphenamine *sufficiently large to stop the activity of the spirochaete in the somatic tissues* was responsible I emphasize the importance of the size of the dose of "606", because it affects the development of anti-treponemal substances which would restrain the activity of residual nests in the coats of the cranial nerves and such-like places

These views were later supported by the experience of one of the five American clinics which participated in the American Cooperative Clinical Studies (Moore and others, 1932) In this it was stated that at Clinic B, out of thirteen clinical relapses no fewer than five were of the neuro-recurrent type, and it was admitted that Clinic B differed from the others particularly in withholding heavy metal during the first course If the advice of Neisser had been followed those neuro-recurrences would not have occurred

Thus I think that Neisser has proved to be fully justified in his early insistence on the concurrent use of heavy metal with arsphenamine treatment and, as I said earlier, his stand on this point, fortified

* Kolle (1918) and Kolle and Ritz (1919)

* In my report I said 59 the correct figure was 58

with all the power which his reputation for sound scientific wisdom endowed it, must have influenced the treatment of very many thousands of patients and must in this way have prevented an incalculable amount of harm through syphilitic neuro-recurrence

I am conscious that, in this address, I have paid only a feeble tribute to Neisser's great service to mankind, but perhaps others better versed in medical history than I am will adequately supplement what I have said

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CARDIOVASCULAR SYPHILIS
A CLINICAL STUDY OF 578 CASES*

BY

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Review of the Literature

With the perfection of penicillin schedules and improved epidemiological procedures during World War II and the ensuing years, the incidence of early syphilis has reached its lowest level It is feared that, as interest in early syphilis wanes because of its relative scarcity, interest in late syphilis will also diminish This would be unfortunate, since there are 2,100,000 persons in the United States with undetected or inadequately treated syphilis (U S Publ Hlth Service, 1953) With the present promiscuous use of penicillin, persons with masked syphilis may develop lesions of late syphilis through inadequate therapy There seems to be general agreement with the opinion expressed by one group (Diseker and others, 1944) that adequate metal chemotherapy of early and latent syphilis prevented the appearance of cardiovascular lesions, but we feel that though it markedly decreased late syphilitic involvement, it by no means halted progression in all patients

For the purposes of this study we have classified cardiovascular syphilis into three main categories aortitis, aneurysm, and aortic insufficiency Coronary ostial involvement is also considered as it occurs as a complication of these conditions, other less frequently encountered lesions of the cardiovascular system will be considered briefly

The earliest and most important phase of cardiovascular involvement is uncomplicated aortitis, since it is at this stage that we believe adequate penicillin therapy can prevent further progression of the lesion One investigator (Howe, 1943) is of the opinion that adequate arsenic and bismuth therapy accomplished this purpose, but others (Hood and Mohr, 1937) felt that such treatment was of little value

The diagnosis of syphilitic aortitis is not easy, the reported incidence of cardiovascular involvement in patients having latent and late syphilis on a histological basis varies from 40 per cent (Rosahn, 1946, Peters and others, 1955) to 70 to 90 per cent (Warthin, 1931), while only 10 per cent of patients with untreated late syphilis develop clinically manifest cardiovascular lesions (Bruusgaard, 1929) More careful screening of patients with latent and late syphilitic involvement of other systems should result more frequently in the correct diagnosis of cardiovascular involvement

Opinion varies regarding the presence of diagnostic symptoms in uncomplicated aortitis Kampmeier and others (1942) feel that the condition is completely symptomless, but we are in accord with those who feel that non-radiating substernal pain unrelated to exertion and/or symptoms of diminished cardiac reserve (in the absence of hypertension and valvular disease) is present in some patients with aortitis (Mattman and Moore, 1943) Nor is there any agreement concerning diagnostic physical findings in this condition An aortic systolic murmur has been considered significant (Maynard, 1942), but we are in agreement with Moore and others (1943) that an accentuated aortic second sound of characteristic tambour quality, in a patient without hypertension or arteriosclerosis, is the only significant physical finding Lucia and Sears (1946) say that uncomplicated aortitis cannot be diagnosed with any degree of certainty on the basis of physical findings

Kemp and Cochems (1937) noted x-ray evidence of aortic dilatation in 59 per cent of a group of patients with clinically evident syphilitic aortitis utilizing routine postero-anterior views After comparison of the postero-anterior chest films of large numbers of syphilitic and non-syphilitic patients, using the technique of aortic measurement of Vaquez and Bordet (1920), they concluded that there was no difference between the degree of aortic widening due to hypertension, arteriosclerosis, and the ageing process in syphilitic patients without clinically evident cardiovascular involvement and

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that in non-syphilitic patients Similar findings were reported by Boharas and others (1942) Moore (1949) has stated that aortic measurements are of little value unless marked distortion is present, and the routine use of fluoroscopy, anterior oblique films, or rontgen kymography has been recommended for diagnostic purposes The left anterior oblique view is particularly valuable in delineating the ascending aorta Calcific deposits in the aorta were felt by Blumenthal and others (1944) to be due more frequently to hypertension and arteriosclerosis than to syphilis Leighton (1948) and Jackman and Lubert (1945) thought that linear calcification, particularly in the ascending aorta, was pathognomonic of syphilitic aortic involvement Though this was not usually an early sign of involvement, it was valuable in the differential diagnosis of aortic insufficiency We feel that the importance of this finding as a diagnostic aid has not received enough emphasis in practice The technique of angiocardiography described by Robb and Steinberg (1938) has been helpful in the early recognition of cardiovascular syphilis (Dotter and Steinberg, 1949) This procedure permits visualization of the first portion of the aorta, which is usually obscured by the heart shadow in routine *x*-ray studies, but unfortunately does not lend itself to application in an out-patient clinic

Cole and Bohning (1944) and Berk (1941) were unable to demonstrate any specific electrocardiographic changes in uncomplicated aortitis

Spread of the syphilitic process proximally with resultant weakening of the media produces dilatation of the aortic root and, consequently, dilatation of the aortic ring This dilatation is the basis for regurgitation in the earliest stage of aortic valvular insufficiency An interesting case of this type has been found at autopsy (Massachusetts, 1941) At this stage the aortic second sound may be discernible, followed by a short, very faint diastolic murmur Involvement of the valve resulting in deformity of the cusps and widening of the valve commissures is a later development Extension of the elastic fibres of the media proximal to the attachment of the cusps has been observed in some patients (Wilens, 1940) This variation seemed to have a definite bearing upon the degree of regurgitation

The commonest symptoms in aortic insufficiency, when present, are exertional dyspnoea and paroxysmal nocturnal dyspnoea Precordial pain is usually evidence of coronary ostial involvement (Bruenn and others, 1936), though aortic insufficiency with a lowered diastolic blood pressure may result in diminished coronary circulation and anginal symptoms with essentially normal ostia There may be little, if any, correlation of ECG changes and precordial pain (Blackford and Smith, 1938) Aortic insufficiency may exist in an asymptomatic phase for a variable period (McDermott and others, 1942)

The murmur of aortic insufficiency has been described (White, 1944) as a blowing diastolic aortic murmur, decrescendo in nature Auscultation is facilitated by the use of a diaphragm stethoscope, with the patient leaning forward in a sitting position and holding his breath after full expiration Maximal intensity may be over the left sternal border in the third and fourth intercostal spaces or over the right lower sternal margin, depending upon the position of the heart *Transmission of the* murmur may be to the apex, left axilla, or neck Rarely, the murmur may have a musical or " dovecote ' quality and may be of such intensity as to be heard without a stethoscope some distance from the patient Such was the case in two of our patients The pathological basis of this murmur may be a ruptured or perforated aortic cusp (Wilbur, 1941) or merely retroversion of a valve leaflet (Bellet and others, 1939)

A presystolic apical murmur (Austin Flint) has frequently been reported in patients with aortic insufficiency (Nicol, 1950), but Luisada (1944) felt that true Austin Flint murmurs were uncommon

The more prominent peripheral findings of advanced aortic regurgitation are the water-hammer or " Corrigan " pulse and a capillary pulse detected in the nail bed or mucous membrane of the lips Durozïez's sign is frequently encountered Peripheral signs may be entirely lacking in the early stages and in patients with a normal pulse pressure

X-ray evidence of left ventricular hypertrophy was demonstrated in 93 per cent of a group of patients with aortic insufficiency due to syphilis (Nichols, 1940), however, this finding may be minimal or absent in early cases and in those without peripheral signs The diagnostic importance of linear calcification in the ascending aorta has been mentioned previously Left axis deviation is a common electrocardiographic finding The T-wave and S-T segment changes, so frequently seen in advanced aortic insufficiency, have usually been attributed to myocardial hypertrophy rather than to coronary involvement (Parsonnet and Bernstein, 1943)

The differential diagnosis of aortic insufficiency may be a difficult matter, this problem arises in distinguishing syphilitic from rheumatic lesions Bacterial endocarditis, congenital cardiac lesions, arteriosclerosis, and calcific disease of the aortic valve must also be ruled out

The importance of a careful history cannot be overemphasized A history of murmur present since childhood may sometimes be obtained, and frequently a history typical of rheumatic fever or symptoms suggestive of the so-called "rheumatic state" Rheumatic heart disease usually becomes clinically evident earlier in life (20 to 35 years of age) Rheumatic aortic involvement commonly produces a stenotic lesion in addition to insufficiency and, quite often, mitral stenosis co-exists Radiological examination in these patients may reveal left auricular enlargement As a rule, x-ray and fluoroscopic examinations fail to reveal dilatation of the aorta in lesions of rheumatic origin Auricular fibrillation has been reported as very unusual in syphilitic heart disease (Comeau, 1942), although contradictory findings substantiated at autopsy have been presented (Plice and Pfister, 1949) and the conclusion has been drawn that auricular fibrillation is almost as common in syphilitic heart disease as in other cardiac conditions Bacterial endocarditis complicating aortic insufficiency strengthens the probability of a rheumatic aetiology, though this complication is rarely noted in syphilitic aortic valvulitis (Braunstein and Townsend, 1940) In addition, cases of combined syphilitic and rheumatic valvular disease have been reported by Plice and Edinburg (1942) and by Lisa and others (1942) The serologic test for syphilis (STS) is usually negative in rheumatic heart disease It must be emphasized, however, that a negative STS does not rule out the diagnosis of syphilitic heart disease Beckh (1943) found 4 per cent of a group with proven syphilitic heart disease to be sero-negative, and Kampmeier (1938) found a positive STS or history of previous treatment in only 86 per cent of a large group of patients with aortic aneurysm

Varying degrees of arteriosclerosis are often associated with syphilitic involvement in older patients, though valvular insufficiency due to arteriosclerosis is a rare occurrence (Epstein, 1938) Seven per cent of a group of patients with syphilitic aortic insufficiency also exhibited at autopsy aortic stenosis due to calcification of the aortic valves (Woodruff, 1948)

Involvement of the coronary arteries may occur at any stage of cardiovascular syphilis, but is most commonly associated with aortic insufficiency (Burch and Winsor, 1942) The syphilitic process is usually limited to the coronary ostia, but a case has been reported by Strassmann and Goldstein (1942) which, at autopsy, showed involvement of the entire length of the coronary artery Coronary involvement is a finding more frequent in those cases with an anomalous origin of the coronary arteries distal to the aortic ring (Von Glahn, 1923) Marked narrowing of the ostia usually produces myocardial fibrosis occasionally resulting in myocardial infarction (Fisch and Rosenbaum, 1950, Norris, 1937) Cole and Bohning (1944) described three cases with the typical electrocardiographic findings of anterior infarction Bundle branch block has been considered as indicative of coronary obstruction (Sprague, 1942), though this finding may result from myocardial hypertrophy with essentially normal coronaries (Rasmussen and Moe, 1948) Myocardial infarction secondary to thrombosis or embolism on a syphilitic basis may occur (Pratt-Thomas, 1943, Volk and others, 1950)

The most frequent site of syphilitic aneurysm is the ascending aorta, the occurrence being progressively less frequent in the more distal portions Signs and symptoms, when present, are primarily due to aneurysmal pressure on adjacent structures Dysphagia results from compression of the oesophagus, while involvement of the recurrent laryngeal nerve may give rise to hoarseness, aphonia, or a typical brassy cough Compression of the trachea or a bronchus may produce stridor, and, if bronchial compression is marked, it can produce atelectasis Horner's syndrome has occasionally been due to aneurysmal pressure on the superior thoracic sympathetic chain The classic picture of the superior vena cava syndrome secondary to an aortic aneurysm is a possibility (Hinshaw and Rutledge, 1942) and aneurysmal compression of the pulmonary artery has been known to cause embarrassment of the pulmonary circulation (Brill and Jones, 1946) Bone pain is due to erosion of the ribs and sternum or the vertebral column Neurological signs, such as cord bladder, can result from aneurysmal compression of the spinal cord (Shimkin, 1939)

An aneurysm of the ascending aorta may produce dullness to percussion to the right of the sternum Visible pulsation in the right second and third interspaces is sometimes apparent Large aneurysms in this region produce a prominence of the right anterior chest wall Aneurysm of the arch may present as a pulsatile mass in the suprasternal notch, and tracheal tug can be elicited in some cases Rarely, an aneurysm in this region may impinge on the great vessels arising from the arch, causing diminished pulsation in the neck or a discrepancy of the pulse or blood pressure in the arms (Maynard, 1942) Aneurysm of the descending thoracic and abdominal aorta are as a rule devoid of signs and symptoms

Thrombus formation in the aneurysmal sac accompanied by fibrosis and deposition of calcium

in the wall of the sac greatly improves the outlook When these events fail to occur, the possibility of aneurysmal rupture is always present The sac may rupture into a bronchus (Massachusetts, 1941), pulmonary artery (Scott, 1924), superior vena cava (Armstrong and others, 1949), the pleura or pericardium (Goldstein, 1949), or rarely into the right ventricle (Harris and Schattenberg, 1944), with bizarre terminal physical findings

The reported frequency of syphilitic aneurysm of the abdominal aorta varies from 9 per cent (Mills and Horton, 1938) to 74 per cent (Scott, 1944) in pathological studies to determine the aetiology of abdominal aneurysms Scott concluded that aneurysms above the origin of the renal artery were most often syphilitic In approximately 34 per cent of the syphilitic group an aneurysm of the thoracic aorta was also present, and an additional 18 per cent also had aortic regurgitation

While it is well to be aware of the signs and symptoms attributable to aortic aneurysms, it should be emphasized that in many instances this condition is entirely symptomless and diagnosis depends solely upon adequate radiological examination

Rarely encountered conditions of the cardiovascular system due to syphilis include involvement of the pulmonary arteries (Boyd and McGavack, 1939), the great vessels arising from the arch of the aorta (Barker, 1949), the hepatic artery (Malloy and Jason, 1942), and the renal artery (Price and Skelton, 1948) Additional findings are those of aneurysm of the heart (Cookson, 1929), as well as of the sinuses of Valsalva (Chipps, 1941 , Ostrum and others, 1938) and the coronary arteries (O'Neill and Lainply, 1949 , Snyder and Hunter, 1934)

Syphilitic myocarditis is considered rare (Saphir, 1942), but others think that this condition should be considered in the differential diagnosis of any syphilitic patient who develops moderate decompensation or other unexplained cardiac symptoms (Rasmussen and Moe, 1948 , Magill, 1935) A case of interventricular block of short duration which developed under observation and disappeared after antisyphilitic therapy (Nolan and Pedigo, 1946) lends support to the latter idea Another rare finding, gumma of the myocardium, should be suspected in cases where radiological examination reveals unexplained shadows at the cardiac margins (Sohval, 1935)

The general feeling is that uncomplicated syphilitic aortitis without coronary ostial involvement carries a good prognosis In one series of 105 patients diagnosed at autopsy, only 24 had died of causes related in any way to syphilis, and only ten of these died as a probable direct result of aortic involvement (Moore, 1949) On the other hand, prognosis in aortic insufficiency and aneurysm is said to be poor after the onset of symptoms (average $1\frac{1}{2}$ years) and especially so after the appearance of congestive failure (Montgomery and others, 1952) In one group, however, the asymptomatic phase of syphilitic aortic insufficiency ranged from 2 to 10 years (average 6) and survival after the onset of symptoms was 2 to 14 years (average 5 to 6) (Reader and others, 1947) Survival after the appearance of symptoms in patients with untreated aneurysm in another series was 1 to 3 years (average 19 months) (Moore and others, 1943)

The reported results obtained by adequate treatment of cardiovascular syphilis vary , some feel treatment to be of little or no value in prolonging life and halting progression of the disease process (Kampmeier and Combs, 1940), while others believe such therapy to be definitely beneficial (Jensen, 1942 , Barnett and Small, 1950)

In a series of recent publications (Padget and others, 1950 , Densen and others, 1952 , Webster and others, 1953), the problem of therapy evaluation in cardiovascular syphilis has been analysed exhaustively with respect to the medical, statistical, and methodological problems involved , the weaknesses inherent in most of the past attempts to evaluate therapy are pointed out, and the prerequisites for a valid analysis of penicillin therapy in cardiovascular syphilis are demonstrated

In spite of the lack of statistically sound analyses, in practice, in the United States, penicillin has been increasingly used as the specific drug in all types of cardiovascular syphilis The experience of various groups (Stokes and others, 1951 , Sinclaire and Webster, 1954 , Eisenberg and Brandfonbrener, 1953a, b , Edeiken and others, 1953) is reflected in the general recommendation of penicillin (U S Publ Hlth Service, 1953 , Curtis and others, 1951)

The possibility of adverse reactions, such as those of Herxheimer (Butterly and Fishman, 1952 , Diefenbach, 1949 , Whorton and Denham, 1951) and the " therapeutic paradox ' (Mohr and Hahn, 1952 , Porter, 1948), necessitated caution in the use of penicillin, but these untoward reactions rarely have been encountered in patients with cardiovascular syphilis (Tucker and Farmer, 1947 , Edeiken and others, 1949, 1950 , Russek and others, 1946, 1949 , Flaum and Thomas, 1949 , Sinclaire and Webster, 1951)

Clinical Study

Against this background of previous experience, our experiences with the treatment of cardiovascular

TABLE I

TOTAL SERIES OF CARDIOVASCULAR PATIENTS BY ORIGINAL DIAGNOSIS AND FINAL DISPOSAL*

Original Diagnosis	Disposal					Total with Cardiovascular Diagnosis
	Verified Final Outcome			Unverified		
	Living and Observed	Dead	Total	Living and Not Observed	Unknown	
Syphilitic Aortitis	162	98	260	59	51	370
Syphilitic Aortic Regurgitation	37	73	110	8	14	132
Syphilitic Aneurysm	13	31	44	4	9	57
Syphilitic Aortic Regurgitation and Aneurysm	4	14	18	—	1	19
Totals	216	216	432	71	75	578

*All patients diagnosed before 1947 in Chicago Health Department Clinics and final classification made in 1952

syphilis in the venereal disease control program of the Chicago Board of Health are here reported

The series comprises 578 patients in whom cardiovascular syphilis was diagnosed before 1947 A breakdown of the series by particular diagnosis and outcome is given in Table I A patient who could not be located was listed as unknown only after a thorough check of both city and State files had failed to place him as dead All patients used for comparison had a follow-up of 5 years or more, and those living but not observed are included only in the consideration of longevity

The majority of these patients were referred to the cardiovascular section because of some abnormality discovered on routine physical examination in the general venereal disease clinic The cardiovascular examination consisted of

(1) Complete cardiac history and physical examination,

(2) radiological examination, originally consisting of routine postero-anterior x-ray, supplemented by fluoroscopy in a small percentage of patients and, more recently, by right and left anterior oblique views,

(3) electrocardiography until 1947 this consisted of the three standard leads and CF_4, it now includes the three standard leads, V_1–V_6, and the AV leads

The majority of patients living and observed were examined approximately every 6 months, and repeat *x*-rays and electrocardiographs were taken at yearly intervals as nearly as possible Some in this group, however, lapsed from observation and may have had only an initial examination, with a repeat in the past year

Most patients after diagnosis of cardiovascular involvement received prolonged bismuth therapy Bismuth (150 mg) was administered weekly for a 10-week period and repeated at least once and, often, two or three times yearly Some of the group received arsenical therapy, and, in more recent years, penicillin has been administered to a few patients

The diagnosis of uncomplicated syphilitic aortitis was based on the presence of at least two of the following criteria

(1) typically accentuated tambour like aortic second sound, either with or without an associated soft systolic aortic murmur,

(2) history of chest pain, usually dull substernal pain unrelated to exertion, or symptoms of diminished cardiac reserve in the absence of hypertension, arteriosclerosis, or other clinically evident cause,

(3) *x*-ray evidence of widening of the supracardiac shadow,

(4) positive STS, history of a previously positive STS, and/or previous antisyphilitic therapy

Syphilitic aortic regurgitation was diagnosed on the basis of the typical aortic diastolic murmur in patients with a negative history of rheumatic disease and in the absence of radiological findings suggesting a co-existent mitral valvular lesion

Syphilitic aortic aneurysm was diagnosed on the basis of radiological findings

Comparisons were made of the influence upon prognosis of a number of variables

The influence of race, sex, and age at diagnosis can be seen in Table II (opposite)

Race.—In the group with aortitis, prognosis was significantly poorer for the white males At final evaluation 5 years or more after original diagnosis, 36 1 per cent were living and 63 9 per cent were dead among the white males, as compared with 62 9 per cent living and 37 1 per cent dead among the Negro males In the group with aortic regurgitation and/or aneurysm, prognosis was slightly poorer for white males, 21 3 per cent living and 78 7 per cent dead, as against 29 3 per cent living

TABLE II

DISPOSAL OF PATIENTS HAVING CARDIOVASCULAR SYPHILIS BY AGE AT ORIGINAL DIAGNOSIS RACE, AND SEX

Sex	Cardiovascular Diagnosis	Age (yrs)	Grand Total					Race								
								White					Negro			
			Total Cases	Living and Observed		Dead		Total Cases	Living and Observed		Dead		Total Cases	Living and Observed		Dead	
				Number	Per cent	Number	Per cent		Number	Per cent	Number	Per cent		Number	Per cent	Number	Per cent
Male	Syphilitic Aortitis	Under 50	82	51	62 2	31	37 8	8	5	62 5	3	37 5	74	46	62 2	28	37 8
		50 and over	70	35	50 0	35	50 0	28	8	28 6	20	71 4	42	27	64 3	15	35 7
		All ages	152	86	56 6	66	43 4	36	13	36 1	23	63 9	116	73	62 9	43	37 1
	Aortic Regurgitation and/or Aneurysm	Under 50	66	16	24 2	50	75 8	22	5	22 7	17	77 3	44	11	25 0	33	75 0
		50 and over	73	21	28 8	52	71 2	25	5	20 0	20	80 0	48	16	33 3	32	66 7
		All ages	139	37	26 6	102	73 4	47	10	21 3	37	78 7	92	27	29 3	65	70 7
Female	Syphilitic Aortitis	Under 50	67	50	74 6	17	25 4	11	10	90 9	1	9 1	56	40	71 4	16	28 6
		50 and over	41	26	63 4	15	36 6	14	8	57 1	6	42 9	27	18	66 7	9	33 3
		All Ages	108	76	70 4	32	29 6	25	18	72 0	7	28 0	83	58	69 9	25	30 1
	Aortic Regurgitation and/or Aneurysm	Under 50	22	13	59 1	9	40 9	5	5	100 0	—	—	17	8	47 1	9	52 9
		50 and over	11	4	36 4	7	63 6	5	2	40 0	3	60 0	6	2	33 3	4	66 7
		All Ages	33	17	51 5	16	48 5	10	7	70 0	3	30 0	23	10	43 5	13	56 5

and 70 7 per cent dead among the Negro males Since these differences among patients with more severe cardiovascular involvement are not statistically significant, the findings do not suggest to us a peculiar racial susceptibility

Sex—In both diagnostic groups, those with syphilitic aortitis and those with aortic regurgitation and/or aneurysm, the prognosis for females was significantly better than that for males in both races These findings concerning sex may reflect the deleterious effect of heavy manual labour upon prognosis among patients with cardiovascular syphilis

Age—With the exception of Negro males, the prognosis was better for persons under 50 years of age at time of diagnosis in each race-sex group in both diagnostic categories However, since none of these differences by age proved to be statistically significant, the higher death rate among older patients probably only reflects the normally higher death rate in an ageing population

No particular difference is noted in the prognosis of those receiving adequate or inadequate treatment in either diagnostic category (Table III) The larger percentage of patients living among those treated with penicillin is based on a comparatively small number of patients Furthermore, because of the comparatively short period before 1947 during which penicillin was available for the treatment of syphilitic cardiovascular disease, the final disposition was made in many cases shortly after the 5-year minimum follow-up period, which, in the penicillin group, would weight the outcome in favour of those living at final evaluation

The status of the serologic test for syphilis at time of diagnosis does not appear to influence the prognosis in either diagnostic category (Table IV, overleaf) No significant differences could be demonstrated in the syphilitic aortitis group between the 64 5 per cent living of sero-positive cases and the 76 9 per cent living of sero-negative cases Similarly, the 32 5 per cent living of those who were sero-positive when diagnosed with aortic regurgitation and/or aneurysm is not significantly different from the 22 2 per cent living of sero-negative cases Of the 228 cases who were sero-positive at the time of diagnosis with syphilitic aortitis, 110 (48 2 per cent) had attained sero-negativity at final evaluation, and of the 160 cases who were sero-positive at the

TABLE III

RESULTS OF CARDIOVASCULAR SYPHILIS BY ORIGINAL DIAGNOSIS AND TREATMENT

Original Diagnosis	Treatment	Total Cases	Result			
			Living and Observed		Dead	
			Number	Per cent	Number	Per cent
Syphilitic Aortitis	Inadequate	151	85	56 3	66	43 7
	Adequate*	69	41	59 4	28	40 6
	Penicillin	40	36	90 0	4	10 0
	Total	260	162	62 3	98	37 7
Aortic Regurgitation and/or Aneurysm	Inadequate	134	39	29 1	95	70 9
	Adequate*	33	11	33 3	22	66 7
	Penicillin	5	4	80 0	1	20 0
	Total	172	54	31 4	118	68 6

* Adequate treatment for this series consisted of more than twenty arsenical and thirty or more bismuth injections

TABLE IV

RESULTS OF PATIENTS HAVING CARDIOVASCULAR SYPHILIS BY ORIGINAL DIAGNOSIS AND SEROLOGICAL STATUS AT TIME OF DIAGNOSIS

Original Diagnosis	Serological Status	Total Cases	Result			
			Living and Observed		Dead	
			Number	Per cent	Number	Per cent
Syphilitic Aortitis	Positive	228	147	64 5	81	35 5
	Negative	13	10	76 9	3	23 1
	Unknown	19	5	26 3	14	73 7
	Total	260	162	62 3	98	37 7
Aortic Regurgitation and/or Aneurysm	Positive	160	52	32 5	108	67 5
	Negative	9	2	22 2	7	77 8
	Unknown	3	—	—	3	100 0
	Total	172	54	31 4	118	68 6

time of diagnosis with aortic regurgitation and/or aneurysm 64 (40 per cent) were sero-negative at final evaluation

Among those originally diagnosed with syphilitic aortitis, 39 were diagnosed with cardiovascular progression either before or at final disposition Table V shows that twelve out of 25 of the cases living and observed at final disposition had progressed from aortitis to aortic regurgitation and/or aneurysm more than 7 years after the original diagnosis, and that nineteen of this group had progressed more than 5 years after the original diagnosis Patients in whom uncomplicated aortitis has been present for a long time may still develop aortic insufficiency or aneurysm after therapy since damage to the media and aortic valves may have occurred before the causative agent could be eradicated

X-ray and electrocardiographic findings by diagnosis are presented in Table VI The λ-ray findings re-emphasize the ascending aorta as the site of predilection for syphilitic infection of the

TABLE V

INTERVAL BETWEEN ORIGINAL DIAGNOSIS OF SYPHILITIC AORTITIS AND PROGRESSION TO AORTIC REGURGITATION AND/OR ANEURYSM BY FINAL DISPOSITION

Disposal		Interval from Diagnosis to Progression (yrs)					Total Number of Progressions
		2 or less	3 to 5	6 to 7	8 to 9	10 or more	
Living and Observed	Number	3	3	7	10	2	25
	Cumulative percentage	12 0	24 0	52 0	92 0	100 0	—
Dead	Number	8	5	1	—	—	14
	Cumulative percentage	57 2	92 9	100 0	100 0	100 0	—
Total	Number	11	8	8	10	2	39
	Cumulative percentage	28 2	48 7	69 2	94 9	100 0	—

TABLE VI

λ RAY AND ELECTROCARDIOGRAPHIC FINDINGS IN CARDIOVASCULAR SYPHILIS

	Findings	Diagnosis				Total
		Aortitis		Aortic Regurgitation and/or Aneurysm		
		Living and Observed	Dead	Living and Observed	Dead	
λ Ray	Dilatation: Ascending aorta	92	53	28	65	238
	Dilatation: Descending aorta	2	—	2	2	6
	Dilatation: Both branches of aorta	61	22	20	18	121
	Left ventricular hypertrophy	47	36	34	81	198
	Linear calcification ascending aorta	35	9	10	15	69
	Aneurysm: Ascending aorta or arch	7	5	12	39	63
	Aneurysm: Descending aorta	5	—	7	6	18
	Aneurysm: Ascending and descending aorta	—	—	—	3	3
	Aneurysm: Innominate artery	—	2	1	2	5
	Aneurysm: Heart	—	—	1	—	1
	Normal	—	2	—	1	3
	Not done	1	18	—	9	28
	Number in Group	162	98	54	118	432
Electrocardiographic	Left axis deviation	106	32	24	39	201
	Left ventricular preponderance	9	5	9	13	36
	Infarction	6	6	2	—	9
	Auricular ventricular block	6	3	8	8	25
	Extrasystoles: Auricular	2	—	1	7	10
	Extrasystoles: Ventricular	9	3	6	10	28
	S-T deviations only	—	—	1	—	1
	T-Wave changes	49	25	20	59	153
	Abnormal QRS (interventricular block, etc)	3	1	3	10	17
	Auricular fibrillation	—	—	—	1	1
	Abnormal P waves	23	6	7	11	47
	Normal	29	15	8	16	68
	Not done	3	26	—	12	41
	Number in Group	162	98	54	118	432

TABLE VII

INTERVAL BETWEEN PRIMARY SYPHILIS INFECTION AND CARDIOVASCULAR DIAGNOSIS

Diagnosis	Disposal		Interval (yrs)				Interval of Infection	
			10 or less	11 to 19	20 to 30	More than 30	Known	Unknown
Syphilitic Aortitis	Living and Observed	Number	10	18	14	12	54	108
		Cumulative percentage	18 5	51 9	77 0	100 0	—	—
	Dead	Number	6	15	9	6	36	62
		Cumulative percentage	16 7	58 3	83 3	100 0	—	—
	Total	Number	16	33	23	18	90	170
		Cumulative percentage	17 8	54 4	80 0	100 0	—	—
Aortic Regurgitation and/or Aneurysm	Living and Observed	Number	—	5	8	6	19	35
		Cumulative percentage	0	26 3	68 4	100 0	—	—
	Dead	Number	3	22	18	10	53	65
		Cumulative percentage	5 7	47 2	81 1	100 0	—	—
	Total	Number	3	27	26	16	72	100
		Cumulative percentage	4 2	41 7	77 8	100 0	—	—

TABLE VIII

COMPARISON OF PRECORDIAL PAIN T WAVE AND/OR QRS CHANGES AND CARDIAC DECOMPENSATION BY DISPOSAL

Signs or Symptoms	Disposal		Interval between Onset and Disposal for Patients with Cardiovascular Syphilis (yrs)					Total Number of Patients with Specified Signs or Symptoms
			1 or less	1 to 2	3 to 4	5 to 6	7 or more	
Precordial Pain	Living and Observed		8	1	5	9	8	31
	Dead	Number	14	9	17	15	7	62
		Cumulative percentage	22 6	37 1	64 5	88 7	100 0	—
	Total		22	10	22	24	15	93
T-Wave and/or QRS Changes	Living and Observed		40	4	15	14	9	82
	Dead	Number	9	34	27	12	6	88
		Cumulative percentage	10 2	48 9	79 5	93 2	100 0	—
	Total		49	38	42	26	15	170
Cardiac Decompensation	Living and Observed		2	5	3	2	3	15
	Dead	Number	44	6	6	1	2	59
		Cumulative percentage	74 6	84 7	94 9	96 6	100 0	—
	Total		46	11	9	3	5	74

Total number in group Living and Observed 216 Dead 216

cardiovascular system The electrocardiographic abnormalities were not specific for cardiovascular syphilis

Of the ninety patients with aortitis in whom the primary infection was reported, 49 (54 4 per cent) showed cardiovascular involvement less than 20 years after the infection Aortic regurgitation and/or aneurysm was diagnosed less than 20 years after infection in thirty (41 7 per cent) of the 72 patients in whom the time of infection was known (Table VII) The fact that so many of those with known intervals of infection in both diagnostic categories showed cardiovascular involvement less than 20 years after infection (48 8 per cent) indicates that this condition should be searched for in younger patients than is usually the practice

Table VIII shows for the whole series the duration before final result (observation or death) of three factors precordial pain, T-wave and/or QRS changes, and cardiac decompensation This information was collected chiefly for the purpose of estimating the duration of these factors before death, and the cumulative percentages have been computed only for those known to have died Precordial pain was present in 93 (21 5 per cent) of the 432 patients in the series and to date 62 of these patients have died Death occurred within 1 year of onset of symptoms for 22 6 per cent, within 2 years for 37 1 per cent, and within 4 years for 64 5 per cent In the majority of patients this symptom was more probably due to syphilitic involvement of the coronary ostia T-wave and/or QRS changes were noted in 170 (39 4 per cent) of this group, of the 88 who died after these changes were noted, 10 2 per cent died within 1 year, 48 9 per cent within 2 years, and 79 5 per cent within

4 years Cardiac decompensation occurred in 74 (17 1 per cent) of the patients and 59 of these have died , death occurred within 1 year after onset of this symptom in 74 6 per cent , within 2 years in 84 7 per cent , and within 4 years in 94 9 per cent These three factors may therefore be said to have definite prognostic implications

An additional finding which indicates the need for careful screening of neurosyphilitic patients is that 73 (41 per cent) of 178 patients in whom a cerebrospinal fluid examination was made were found to be positive

The period of survival after diagnosis can be seen in Table IX (opposite) The group of patients with aortic regurgitation and/or aneurysm lived longer than is generally expected in such cases This discrepancy is no doubt due primarily to the fact that the majority were asymptomatic when the original diagnosis of cardiovascular involvement was made, and that after the diagnosis of cardiovascular syphilis they were instructed to avoid heavy manual labour and undue physical exertion

Life expectancy at various age levels for this group of patients with syphilitic heart disease and for the general population of the United States is compared in Table X (opposite) * It is common knowledge that syphilitic aneurysm or aortic valvular insufficiency shortens the expectation of life, (Shafer and others, 1954a, b) Rosahn (1952) has stated that every form of syphilitic infection is associated with a reduction in life expectancy In our group the decrease would seem to be mainly due to syphilitic cardiovascular involvement, but we must keep in mind the low socio-economic status of these patients, which may also have exerted an adverse effect on longevity

Bismuth alone or in combination with arsenical therapy did not seem to be very effective in halting the progression of the disease or in prolonging life, but the results obtained in the small number of penicillin-treated patients suggest that this form of therapy may have been more effective In our experience with penicillin we have noted many patients who experienced a marked diminution of symptoms as well as improvement in the general feeling of well-being We have not seen a case of fatal Herxheimer reaction in our cardiac clinic There were a few patients in whom an aortic diastolic murmur developed within a year after penicillin therapy, but most probably this deterioration would have occurred without penicillin therapy We feel that pre-treatment with bismuth is unnecessary Penicillin in amounts of 6,000,000 units or more, over a 2- to 3-week period, has proved to be adequate treatment Decompensation or evidence of severe coronary involvement is an indication for hospitalization with adequate medical supervision, in addition to antisyphilitic therapy

* Life expectancy for the study group calculated from the Table of deaths is the average number of years lived by survivors at the beginning of each age period

Discussion

The diagnosis of early uncomplicated aortitis is sometimes difficult, especially in the presence of hypertension or arteriosclerosis, but with increased awareness of the physical and laboratory findings it may now be made more frequently than was previously thought possible At the slightest suspicion of syphilitic involvement, it seems important to treat the case accordingly, rather than to wait for developing valvular insufficiency, aneurysm formation, or *post-mortem* examination to prove the suspicion correct This was proved by the fact that 40 to 60 per cent of patients with untreated or inadequately treated syphilis showed evidence of cardiovascular syphilis at autopsy in the Tuskegee group (Peters and others, 1955)

It is of utmost importance to diagnose and treat these patients early and adequately in order to halt the progressive damage due to the syphilitic process If the disease process in the aorta is halted before marked damage has been done to the elastic fibres of the media, before valvular damage has occurred, or before marked narrowing of the coronary ostia is present, the patient's expectation of life should be unaffected Treatment will be of some value at any stage, though the later in the course of disease the therapy is administered the less helpful it will be The presence of one complication of syphilitic aortitis offers no assurance that further complications will not occur if treatment is delayed or inadequate We feel that adequate penicillin therapy will halt further progression, particularly the development of coronary involvement, and markedly improve prognosis

Summary

The findings presented in this study of 578 patients diagnosed before 1947 as having cardiovascular syphilis are listed below

(1) Treatment with bismuth, alone or in combination with arsenicals, after the diagnosis of cardiovascular syphilis had no apparent effect in prolonging life or preventing the development of further cardiovascular complications

(2) Prognosis was poorer for males than females, and for white males in particular

(3) Progression was more frequent among males than females and among patients with aortitis who were over 50 years of age at the time of diagnosis

TABLE IX

INTERVAL BETWEEN ORIGINAL DIAGNOSIS AND DISPOSAL OF CARDIOVASCULAR SYPHILIS PATIENTS

Diagnosis	Disposal	Interval (yrs)												Total
		Less than 1	1	2	3	4	5	6	7	8	9	10	More than 10	
Aortitis	Living Observed	—	—	—	—	—	2	39	21	19	22	30	29	162
	Living Not Observed	—	—	—	—	—	—	12	9	5	9	7	17	59
	Dead	10	4	13	15	9	8	14	7	7	4	5	2	98
Aortic Regurgitation	Living Observed	—	—	—	—	—	—	3	3	3	7	5	16	37
	Living Not Observed	—	—	—	—	—	—	—	1	—	2	2	3	8
	Dead	7	8	5	8	10	6	9	7	—	4	3	6	73
Aneurysm	Living Observed	—	—	—	—	—	1	5	2	2	2	1	—	13
	Living Not Observed	—	—	—	—	—	—	—	3	—	1	—	—	4
	Dead	3	1	5	2	9	—	4	1	2	2	—	2	31
Aortic Regurgitation and Aneurysm	Living Observed	—	—	—	—	—	—	1	—	—	—	1	2	4
	Living Not Observed	—	—	—	—	—	—	—	—	—	—	—	—	—
	Dead	2	—	5	1	—	3	—	—	2	—	—	1	14
	Total	22	13	28	26	28	20	87	54	40	53	54	78	503

TABLE X

LIFE EXPECTANCY OF SURVIVORS AT BEGINNING OF EACH AGE PERIOD COMPARISON OF CARDIOVASCULAR SYPHILIS PATIENTS WITH GENERAL POPULATION

Age Group	Diagnosis	Race			
		White		Non white	
		Male	Female	Male	Female
30 to 34	Cardiovascular Syphilis	25 92	30 00	21 64	19 87
	Syphilitic Aortitis	25 71	29 44	20 12	20 20
	Aortic Regurgitation and/or Aneurysm	26 07	*	21 18	19 29
	General Population†	38 18	42 75	33 43	36 83
35 to 39	Cardiovascular Syphilis	20 92	25 00	16 83	14 87
	Syphilitic Aortitis	20 71	24 44	15 12	15 20
	Aortic Regurgitation and/or Aneurysm	21 07	*	16 47	14 29
	General Population†	33 61	38 07	29 43	32 72
40 to 44	Cardiovascular Syphilis	16 35	20 00	12 82	11 11
	Syphilitic Aortitis	16 75	17 44	11 67	10 83
	Aortic Regurgitation and/or Aneurysm	16 07	*	13 53	11 67
	General Population†	29 20	33 49	25 72	28 93
45 to 49	Cardiovascular Syphilis	12 84	15 00	8 61	7 12
	Syphilitic Aortitis	13 61	14 44	7 30	6 82
	Aortic Regurgitation and/or Aneurysm	12 31	*	9 43	7 73
	General Population†	25 00	29 03	22 32	25 42
50 to 54	Cardiovascular Syphilis	9 12	10 00	7 65	5 28
	Syphilitic Aortitis	10 31	9 44	6 74	5 00
	Aortic Regurgitation and/or Aneurysm	8 33	*	8 16	5 63
	General Population†	21 08	24 73	19 33	22 24
55 to 59	Cardiovascular Syphilis	5 74	5 91	5 10	3 00
	Syphilitic Aortitis	6 00	5 63	5 53	2 50
	Aortic Regurgitation and/or Aneurysm	5 53	*	5 03	4 00
	General Population†	17 49	20 63	16 75	19 30
60 to 64	Cardiovascular Syphilis	4 29	5 83	4 11	63
	Syphilitic Aortitis	3 18	6 25	*3 89*	*0*
	Aortic Regurgitation and/or Aneurysm	5 50	*	4 21	1 70
	General Population†	14 23	16 75	14 42	16 72
65 to 69	Cardiovascular Syphilis	1 92	3 75	1 05	0
	Syphilitic Aortitis	2 00	3 37	83	0
	Aortic Regurgitation and/or Aneurysm	1 89	*	1 15	0
	General Population†	11 36	13 22	12 51	14 93

*Insufficient data †Expectation of Life United States 1949 Statistical Bulletin Metropolitan Life Insurance Co , November 1951

(4) Syphilitic cardiovascular disease should be searched for in younger patients than hitherto

(5) The high incidence of co-existent involvement of the cardiovascular and central nervous systems is demonstrated

(6) The prognostic value of three factors (precordial pain, T-wave and/or QRS changes, and cardiac decompensation) is suggested

(7) The incidence of hypertension and sero-reversal, and the *x*-ray and electrocardiographic findings are presented

(8) Uncomplicated syphilitic aortitis, if untreated or inadequately treated, shortens the expectation of life

(9) The results obtained after 5 or more years' observation after penicillin treatment of a small group of patients indicate that penicillin is the drug of choice in this condition

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EVALUATION OF CARDIOLIPIN ANTIGEN IN ROUTINE WASSERMANN REACTIONS*

BY

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Cardiolipin is a phospholipid and was isolated by Pangborn (1941, 1942) while investigating the nature of the antigenic material in beef heart muscle used in the Wassermann reaction It was shown that cardiolipin was serologically active when used together with lecithin, and that the sensitivity of the reaction was enhanced by the addition of cholesterol A monograph on cardiolipin antigen was published by Pangborn and others (1951), and details of this antigen and methods of preparation are given

Many publications discuss the value of cardiolipin antigen in complement-fixation tests (CFT) and flocculation tests, and most workers have made a strong case for the adoption of this antigen in order to obtain greater sensitivity and specificity in these tests Mazzini (1951) describes a microflocculation cardiolipin test, and writes that a vast improvement in sero-diagnostic procedures has been made with this antigen, but that there is a tendency to zonal reactions Lundback and Allander (1951) point out that cardiolipin-lecithin-cholesterol antigen is superior to the old crude extract with regard to specificity and probably to sensitivity as well Vogelsang and Haaland (1951) also note that cardiolipin antigen is more specific and offers certain advantages when applied to complement-fixation and flocculation tests The following published reports are also in favour of cardiolipin antigens, particularly with regard to increased specificity and sensitivity Chronicle of the World Health Organization (1951), Joulia and Pautrizel (1951a, b), Flynn, Tompkins, and Beecher (1952), and Steigner (1954) Guthe and Willcox (1954) write, " the more specific cardiolipin antigens have now been accepted everywhere as the antigens of choice in the sero-diagnosis of syphilis " Rappaport and Eichhorn (1951) used a tube flocculation method with three different formulae for the cardiolipin antigen and obtained practically identical results in specificity and sensitivity Giordano, Shively, and Bahler (1952) compared cardiolipin microflocculation VDRL (American) antigen with standard Kolmer CFT antigen used in the Kolmer complement-fixation test, and found that the cardiolipin antigen gave increased sensitivity, but slight loss in specificity They advised cardiolipin antigen for routine use Price and Wilkinson (1950) reviewed the results of over 5,000 complement-fixation tests using cardiolipin and standard antigen (1/15 dilution) in parallel tests With sera from a V D clinic and with routine hospital patients, cardiolipin gave increased sensitivity, but more non-specific results The same authors (1952) again compared a large series using the standard antigen at optimum titre with similar results Nelson and Martin (1954), Klein, Konwaler, and Leiby (1954), and Price (1954) have independently compared complement-fixation tests with standard and cardiolipin antigens, and recorded increased sensitivity but loss of specificity with cardiolipin

Tests at the London Lock and Charing Cross Hospitals

Dr Fawkner-Corbett of the London Lock Hospital commenced parallel testing with cardiolipin and crude heart antigens in March, 1952 When the V D centre closed down late that year, he very kindly passed his records to the author

At the Charing Cross Hospital similar parallel testing of sera was commenced in January, 1953, using the same technique as that used at the Lock Hospital The author was also fortunate in securing the services of Dr Fawkner-Corbett s serological technician The standard antigen was used as in Harrison and Wyler s technique at a dilution of 1/15 in saline , the cardiolipin antigen was made up in accordance with the Burroughs Wellcome Whitechapel formula, and so far each batch has been used at the recommended dilution of 1 in 400 There are obvious physical differences in these antigens at these strengths , the cardiolipin is only very faintly opalescent and during the complement titration is little more destructive of complement than saline

Results —A total of 7,337 sera were compared and the results subdivided into eight groups

(1) Altogether 2 773 sera were compared at the London Lock Hospital The subdivision of the results show that those in disagreement were mainly borderline results , cardiolipin antigen gave results 3 5 per cent

* Received for publication December 8 1954

greater than standard antigen, and *vice versa* in only 0 4 per cent (Table I)

TABLE I

LONDON LOCK HOSPITAL SERA

(March 7 to October 31 1952)

Results		Number of Sera	Per cent
Titres Agree	Both +	125	96 1
	Both ±	55	
	Both −	2 486	
Titres Disagree	C+ S−	5	C > S 3 5
	C± S−	61	
	C+ S±	31	
	S+ C−	nil	S > C 0 4
	S± C−	10	
	S+ C±	nil	
Total tested		2 773	100

C = Cardiolipin antigen S = Standard antigen, + = positive ± = weakly positive − = negative

(2) Sera that were positive at 1 in 10 dilution with either antigen and were quantitatively titrated are compared in Table II With the majority of positives cardiolipin gave a higher titre than standard, the difference in titre was usually one tube This Table, therefore, shows increased sensitivity of cardiolipin antigen with positive tests

TABLE II

LONDON LOCK HOSPITAL SERA

Comparison of Titres Positive at 1 in 10 or More with Cardiolipin or Standard Antigen from 2 773 Sera Tested

Results	*Number of Sera*	*Per cent*
Agree	41	22 7
C>S	119	65 7
S>C	21	11 6
Total	181	100

(3) Table III shows a comparison of the results of tests on sera from 74 new cases of syphilis which gave a positive or weakly positive result with either antigen (Some of these sera were referred from elsewhere, but others were genuine cases of early syphilis) Cardiolipin antigen appears to be more sensitive with new cases

TABLE III

LONDON LOCK HOSPITAL SERA

74 New Cases of Syphilis Positive with Cardiolipin or Standard Antigen

Results		Number of Sera	Total
Agree	Both+	36	52
	Both±	16	
Disagree	C− S−	2	C > S 21
	C± S−	14	
	C+ S±	5	
	S+ C−	nil	S>C 1
	S± C−	1	
	S+ C±	nil	
Total sera		74	74

(4) A similar comparison is shown in Table IV with old treated cases, cardiolipin antigen was more sensitive

TABLE IV

LONDON LOCK HOSPITAL SERA

213 Old Treated Cases of Syphilis Positive with Cardiolipin or Standard Antigen

Results		Number of Sera	Total
Agree	Both+	89	128
	Both±	39	
Disagree	C+ S−	3	C>S 76
	C± S−	47	
	C+ S±	26	
	S+ C−	nil	S>C 9
	S± C−	9	
	S+ C±	nil	
Total sera		213	213

(5) Table V shows a comparison of 1,792 sera from routine patients at the Charing Cross Hospital, excluding antenatal sera

TABLE V

CHARING CROSS HOSPITAL SERA

Comparison of 1 792 excluding Antenatal Sera (January 1 1953 to June 6 1954)

Results		Number of Sera	Per cent
Agree	Both+	66	97 7
	Both±	34	
	Both−	1 650	
Disagree	C+ S−	7	C>S 1 9
	C± S−	19	
	C+ S±	9	
	S+ C−	2	S>C 0 4
	S± C−	2	
	S+ C±	3	
Total tested		1,792	100

(6) From the 1,792 sera in Table V there were 111 known cases of syphilis, many being old treated ones, at the Charing Cross Hospital A comparison is made in Table VI of these sera which gave a positive or doubtful result with either antigen, there was again an increased

TABLE VI

CHARING CROSS HOSPITAL SERA

Comparison of 111 known Cases of Syphilis excluding Antenatal, Positive with Cardiolipin or Standard Antigen

Results		Number of Sera	Totals
Agree	Both+	65	83
	Both±	*18	
Disagree	C+ S−	*4	C>S 24
	C± S−	*15	
	C+ S±	*5	
	S+ C−	*1	S>C 4
	S± C−	nil	
	S+ C±	*3	
Total sera		111	111

*Nearly all old treated cases

sensitivity of cardiolipin antigen with old treated cases as was shown with those of the London Lock Hospital (Table IV)

(7) From the 1,792 sera in Table V, 22 gave results considered as non-specific reactions (Table VII) No history of syphilis was obtained, the Kahn tests were all negative and many of these complement-fixation tests were repeated with similar or negative results (two of these sera were from cases of glandular fever and one from a case of disseminated lupus erythematosus) It will be seen that cardiolipin antigen gave more non-specific reactions with these routine hospital sera

TABLE VII

CHARING CROSS HOSPITAL SERA

22 Cases considered as Non Specific Reactions

Results		Number of Sera
Agree	Both±	12
Disagree	C+ S− C± S− C+ S±	2 3 3
	S+ C− S± C− S+ C±	1 1 nil
Total (non specific)		22

(8) Table VIII shows a comparison of 2,772 antenatal sera tested during the same period at the Charing Cross Hospital A very high incidence of doubtful results is seen with cardiolipin antigen Many of the doubtful results were repeated with the same or negative result and with negative Kahn tests and were considered as non-specific reactions

TABLE VIII

CHARING CROSS HOSPITAL SERA

2 772 Antenatal Sera tested from January 1 1953 to June 9 1954

Results		Number of Sera	Per cent
Agree	Both+ Both± Both−	5 *33 2 633	96 3
Disagree	C+ S− C± S− C+ S±	*21 *67 *6	C>S 3 4
	S+ C− S± C− S+ C±	nil *7 nil	S>C 0 3
Total tested		2 772	100

*Many repeated with same or negative result

Conclusions

From the above Tables showing the results of parallel complement-fixation tests, it may be considered that cardiolipin is undoubtedly a more sensitive antigen with treated cases of syphilis, and is apparently more sensitive with early cases

The increase in non-specific reactions, which was particularly marked with antenatal sera, is a serious disadvantage A further possible disadvantage is that the test usually remains positive after the standard antigen test has become negative in treated cases

With antenatal sera a doubtful cardiolipin result is no longer reported when the standard Wassermann and Kahn tests are both negative

It is very likely that with modification in formula and technique this antigen may become more specific in use and will then have a greater practical value

Summary

An assessment of the value of cardiolipin antigen compared with standard antigen in over 7,000 complement-fixation tests is made Cardiolipin gave increased sensitivity but loss of specificity, non-specific reactions were particularly evident with antenatal sera

I wish to thank Miss G Pierpoint for valuable technical assistance, and also my secretary Miss G Rayner

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COMPARISON OF OXYTETRACYCLINE AND CHLORTETRACYCLINE IN THE TREATMENT OF NON-GONOCOCCAL URETHRITIS*†

BY

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Since the wide-range orally administered antibiotics, aureomycin (Finland and others, 1948) and terramycin (Willcox, 1951 , Willcox and Findlay, 1952), were first reported as effective in non-gonococcal urethritis the question has arisen of their relative efficacy

In a previous paper a comparison was made of the relative efficacy of terramycin, aureomycin, chloramphenicol, sulphonamides, streptomycin, and penicillin in non-gonococcal urethritis (Willcox, 1953) In assessing the failures no attempt was made to distinguish between relapse and re-infection, except that all such occurrences noted after a symptom-free period of 3 months were assumed to be re-infections This period was commonly accepted as an adequate criterion of cure of non-gonococcal urethritis when the disease was treated routinely with sulphonamides As any extension of this interval after treatment with the antibiotics is concerned more with the possibility of masked syphilis than with uncured urethritis it is considered that this arrangement is reasonable and fair The results of this previous study are shown in Table I

TABLE I

COMPARISON OF RESULTS OF TREATMENT OF NON GONOCOCCAL URETHRITIS IRRESPECTIVE OF DOSE, FOLLOW-UP OR PREVIOUS THERAPY

Drug	No Treated	No Followed up	Failed within 3 Months	
			No	Per cent
Terramycin	70	70	14	20 0
Aureomycin	62	60	16	26 7
Chloramphenicol	65	63	23	36 5
Sulphonamides	75	72	27	37 5
Streptomycin	103	95	40	42 1
Penicillin	85	80	36	45 0
Total	460	440	156	35 5 (average)

Thus, clearly, the two most successful drugs were terramycin (oxytetracycline) and aureomycin (chlortetracycline)

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However, closer examination of the data showed that all drugs were more successful in cases not previously treated This is illustrated in Table II in which the failure rates have been cumulated to compensate for differences in the duration of follow-up

TABLE II

CUMULATIVE RE TREATMENT RATFS AT 3 MONTHS IRRESPECTIVE OF DOSE IN PREVIOUSLY TREATED AND PREVIOUSLY UNTREATED CASES OF NON GONOCOCCAL URETHRITIS

Drug	Previously Treated			Previously Untreated		
	Cases Treated	No Failed	Cumulative Percent Failed at 3 Months	Cases Treated	No Failed	Cumulative Percent Failed at 3 Months
Terramycin	25	9	46 2	45	5	12 9
Aureomycin	29	10	63 3	33	6	25 1
Chloramphenicol	29	11	51 4	36	12	43 7
Penicillin	15	10	104 1	70	26	53 3
Streptomycin	41	18	71 9	62	22	53 8
Sulphonamides	20	6	40 0	55	21	63 7
Total	159	64	—	301	92	—

Although it is evident that the results of treatment with the antibiotics were clearly much inferior in previously treated cases than in those untreated the superiority of terramycin and aureomycin in the untreated case was confirmed

Another important factor was the size of the dose which is recorded in respect of terramycin (Willcox, 1954) in Table III

TABLE III

CUMULATIVE FAILURE RATES IN PREVIOUSLY UNTREATED CASES OF NON GONOCOCCAL URETHRITIS GIVEN TERRAMYCIN RELATED TO DOSE

Dose	No Treated	Failed	Cumulative Per cent Failed at 3 Months
Less than 4 g	4	1	50 0
5–6 g	25	4	19 4
Over 6 g	16	0	—
Total	45	5	—

It is thus evident that no true comparison of the antibiotics can be made unless previously untreated patients are selected, the same dose given, and the cumulative failure rates calculated The results of such a comparison are shown in Table IV which gives the cumulative failure rates in previously untreated patients who had received 5–6 g of the orally administered antibiotics * It will be noted that, although terramycin and aureomycin were still superior, the numbers of previously untreated cases which received 5–6 g of the orally administered antibiotics were, in fact, relatively small

TABLE IV
COMPARISON OF CUMULATIVE RE-TREATMENT RATES OF PATIENTS NOT PREVIOUSLY TREATED GIVEN 5–6 g OF THE ORALLY ADMINISTERED ANTIBIOTICS

Drug	No Treated	No Failed within 3 Months	Cumulative Per cent Failed within 3 Months
Terramycin	25	4	19 4
Aureomycin	25	5	25 3
Chloramphenicol	15	4	30 5
Penicillin	70	26	53 3
Streptomycin	62	22	53 8
Sulphonamides	55	21	63 7

Harkness (1953) who reported a series of cases of non-gonococcal urethritis in which the effect of terramycin and aureomycin was compared, found terramycin to be superior It is apparent, however, that in this study no allowances were made for variations in follow-up (" most of the cases under review were observed for at least a month after antibiotic therapy "), and the dose given was not entirely standardized for " in a small number of uncomplicated cases (usually of acute abacterial urethritis) in which resolution appeared incomplete on the fourth day, the course was extended for a further 2 days " Neither is it stated whether the cases under review were previously untreated

It is significant that the statistical analysis in Harkness's paper was confined to 39 cases treated with each drug, there being five failures in the terramycin-treated group and sixteen failures in the aureomycin-treated group Although it was concluded from the application of Fisher's method that " the apparent superiority of terramycin was confirmed ", no allowance was apparently made for variations in follow-up

Present Study

In order to make a stricter comparison of terramycin and aureomycin the series of previously untreated cases of non-gonococcal urethritis which received 5–6 g of these two drugs, as shown in Table IV, has been enlarged A further forty patients were treated with 6 g terramycin, bringing the series total to 65, and a further 82 patients were treated with aureomycin, bringing the total to 107

Marital Status, Age, and Race —Of the 122 newly added cases 53 were married and 69 were single the average age was 30 8 yrs (extremes 18–61), twelve were Negroes and 110 were white

Previous History —Only 45 gave no history of venereal disease, the remaining 77 admitted having had eighty attacks of gonorrhoea, 45 of non-gonococcal urethritis, and seven of syphilis between them Of the twelve Negroes, three denied previous venereal disease, but the remaining nine had had eighteen attacks of gonorrhoea and two of non-gonococcal urethritis between them

Serology —The serum tests for syphilis (Wassermann and VDRL or Kahn) were both negative in 120, the Wassermann reaction was negative and the Kahn or VDRL test positive in two In nine cases the gonococcal complement-fixation test was not done, but out of 113 cases tested it was negative in 105 and positive in eight

Duration of Symptoms —The discharge had been noted by the patient before treatment for 0–3 days in 51, for 4–7 days in 38, for 8–14 days in twenty, for 15–21 days in six, for 22–28 days in one, and for over 28 days in six

Presence of Trichomonas Vaginalis —Trichomonads were tested for in sixteen cases and found in three (18 75 per cent) These three patients were all treated with aureomycin in one the parasite was still present at 2 days and the patient was lost to observation, although the condition was known to have relapsed later, in one the trichomonads disappeared but the urethritis relapsed and was re-treated at 28 days, in one the condition cleared up and remained satisfactory over an observation period of 61 days

Dysuria —This was complained of by fourteen of 32 questioned

Of eighteen married men fifteen (83 3 per cent) admitted extra-marital intercourse

Results

The results of the 65 terramycin-treated cases and the 107 aureomycin-treated cases are shown in Table V (opposite)

At 2–3 months the cumulative failure rate in the two series was the same

Summary

(1) Results of a previously reported study of the efficacy of terramycin, aureomycin, chloramphenicol,

*The usual dose was 1 8 mega units procaine penicillin with aluminium monostearate (PAM) over 3 days of streptomycin 3–4 g over the same time and of sulphonamides 4 g daily for 5–7 days

TABLE V

RESULTS OF TREATMENT OF 65 PREVIOUSLY UNTREATED CASES OF NON-GONOCOCCAL URETHRITIS WITH TERRAMYCIN AND 107 CASES WITH AUREOMYCIN

Follow up	Treatment					
	Terramycin (5–6 g orally)			Aureomycin (5–6 g orally)		
	No Followed up	Failures including Re infections	Cumulative Per cent Failed	No Followed up	Failures including Re infections	Cumulative Per cent Failed
0	65	—	0	107	—	0
1–7 days	62	1	1 6	101	2	2 0
8–14 days	57	4	8 6	91	5	7 5
15–21 days	51	1	10 6	76	3	11 4
22–28 days	49	1	12 6	71	4	17 0
1–2 months	44	3	19 4	65	4	23 2
2–3 months	33	2	25 5	44	1	25 5
Over 3 months	22	8	—	32	9	—

streptomycin, penicillin, and the sulphonamides in the treatment of non-gonococcal urethritis showed the superiority of terramycin and aureomycin Similar claims have been made by other workers

(2) With all the antibiotics personally tested in this previous study the failure rates were higher in previously treated than in previously untreated cases

(3) The failure rates with terramycin were shown to vary according to the dose given

(4) When previously untreated patients given 5–6 g aureomycin or terramycin were compared, terramycin was apparently the more efficacious, but the numbers involved were too small for a valid statistical comparison

(5) The series of previously untreated patients with non-gonococcal urethritis given 5–6 g aureomycin or terramycin was enlarged to 107 treated with aureomycin and 65 treated with terramycin

(6) All relapses and re-infections occurring within 3 post-treatment months were grouped as failures, and incidents occurring after a symptom-free period of 3 months were considered to be re-infections and excluded When the failure rates in this study are cumulated to allow for differences in follow-up the cumulative failure rates at 3 months for the two drugs are the same

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A STUDY OF NON-GONOCOCCAL URETHRITIS, PRESUMABLY VENEREAL IN ORIGIN, BASED UPON 588 INFECTIONS IN 529 PATIENTS*

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This study of non-gonococcal urethritis had three objectives

(1) To obtain an adequate clinical picture of non-gonococcal urethritis,
(2) to determine the aetiology,
(3) to outline a method of treatment

The following definitions were used in this study

Non-Gonococcal Urethritis—All inflammatory processes of the male urethra presumed due to sexual intercourse, which were not caused by *N gonorrhoea*, *H ducreyi*, *T pallidum*, the tubercle bacillus, protozoan, metazoan organisms, fungi, mechanical irritants, or tumours, were classified as non-gonococcal urethritis

Acute Urethritis, Non-Gonococcal—Non-gonococcal urethral infections in which the onset of the disease had occurred less than one month before the first visit to the clinic

Chronic Urethritis, Non-Gonococcal—Non-gonococcal urethral infections in which the onset of the disease had occurred more than one month before the first visit to the clinic

Posterior Non-Gonococcal Urethritis—A diagnosis of posterior urethritis was made when the gross pyuria was seen in two or more glasses of the multi glass urine test

Concurrent Gonorrhoea—This term was limited to that gonorrhoeal infection immediately preceding the onset of the non-gonococcal urethritis

Cure—No patient was considered cured who had not been free of demonstrable discharge and gross pyuria for a minimum of 2 weeks, and who suffered no relapse after heavy drinking, prostatic massage, urethral dilatation, cystoscopy heavy work, sports, or masturbation

Failure—Patients whose urethritis did not respond to one or more courses of antibiotic therapy, and controls whose disease did not subside spontaneously in 8 weeks, were considered failures

Relapse—A patient was considered to have had a relapse when his discharge or gross pyuria recurred following a clinical remission, but before the criteria for "cure" had been met, in the absence of coitus, and obvious evidence of re-infection

Re-Infection—A patient was considered to have a re-infection when his discharge recurred after the criteria for "cure" had been met and a history of coitus elicited, or when an unequivocally new organism could be demonstrated in his discharge, such as the appearance of previously non existent *N gonorrhoea*

MATERIAL AND METHODS

The patients studied were Korean evacuees and personnel from Army and Air Force installations within a 100-mile radius of the 141st General Hospital Referring organizations submitted complete histories, including pertinent data regarding dates of exposure, state of sobriety and previous treatment

In obtaining specimens for culture the urethra was gently milked, the prepuce retracted, the meatal lips separated, and a finely pointed sterile cotton applicator inserted into the globule of pus, care being taken to avoid scraping the urethral walls Three swabs were thus obtained one was examined fresh for protozoa and fungi, the other two were smeared on slides and planted in aerobic and anaerobic media respectively Lankford's chocolate agar (Lankford, 1950) was used to isolate the Neisseria species, eosin methylene blue agar (Difco) to isolate the Gram-negative organisms of the enteric group, and 5 per cent human blood agar plates for the aerobic organisms principally the Gram positive pyogenic group Sensitivity studies were executed using the paper disk method of Bondi, Spaulding Smith, and Dietz (1947)

Patients were instructed to report to the clinic with full bladders, and a standard multi glass urine test was performed at each visit All patients were advised to abstain from alcohol sexual excitement, coitus, heavy work, sports, and vigorous stripping of the urethra Half of the patients were denied coffee, tea, carbonated beverages, and condiments All patients were confined to barracks for the period of observation

For 8 weeks 113 patients were used as controls and observed without treatment

Penicillin was prescribed in doses ranging from 300,000 units twice daily to 600 000 units twice daily for 1 week, streptomycin 0 5 g twice daily for 1 week to 0 5 g twice daily for 2 weeks, chloramphenicol aureomycin, and terramycin were given in weekly

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courses of 250 mg every fourth hour on a 24-hr basis up to a total of 3 weeks All patients receiving chloramphenicol had a complete blood count before therapy, and this was repeated weekly during therapy

Patients were seen at least once weekly until discharged They were then observed in the follow-up clinic at monthly intervals for as long as 1 year

RESULTS

Clinical Observations

Between January 1, 1951, and June 30, 1953, 2,486 cases of urethritis were seen, 1,943 proved to be cases of non-gonococcal urethritis, and 543 of gonorrhoea, a ratio of 3 6 to 1 Of the non-gonococcal infections, collected in 1952, 588 were intensively studied They occurred in 529 individuals, only nine of whom were not Americans Six of the patients were of Asiatic extraction, 78 were Negroes, and 445 Caucasians The youngest was aged 17 years, the oldest 47, 75 per cent were between the ages of 18 and 30 years Only four patients denied exposure, but one of these had a concurrent gonorrhoea A history of concurrent gonorrhoea was given by 101 patients (17 2 per cent), a ratio of 5 8 to 1, 82 patients had had gonorrhoea previously and seventeen non-gonococcal urethritis, 329 had had neither concurrent gonorrhoea nor previous urethritis

The incubation period could be accurately measured in only 435 of the infections studied, 79 had had concurrent gonorrhoea and 356 had not The ranges of the incubation periods for gonorrhoea and non-gonococcal urethritis were identical, but a significantly larger percentage of the concurrent gonorrhoeal infections had an incubation period of 3 weeks or less

Out of 101 patients with concurrent gonorrhoea 76 had no asymptomatic intervals between the completion of treatment for concurrent gonorrhoea and the onset of non-gonococcal urethritis The majority stated, however, that the discharge did change its character following treatment for gonorrhoea and became less purulent and more scanty

Altogether 47 patients, with supposedly uncomplicated gonorrhoea, were observed after receiving 300,000 units penicillin daily for 3 days 23 of these patients (49 per cent) subsequently developed a non-gonococcal urethritis, seventeen had no asymptomatic intervals, six had asymptomatic intervals ranging from 1 to 6 weeks These six, however, had a gross pyuria throughout the asymptomatic period The 24 patients, who did not develop non-gonococcal urethritis, had no gross pyuria following treatment of gonorrhoea

Symptoms and Signs (Table I)—The presence of a concurrent gonorrhoea did not materially influence the character of the symptoms and signs seen in the 588 infections studied In 68 patients with concurrent gonorrhoea the initial discharge decreased in character after treatment of the gonorrhoea with penicillin, in 33 there was no change Of the 68 in whom the discharge decreased in quantity 25 had an asymptomatic interval ranging up to 6 weeks

A discharge was complained of by 572 (97 2 per cent) patients, but it could only be found in 555 (94 4 per cent) Initially, it was profuse and purulent, resembling that of gonorrhoea, but quickly subsided into a thin, scant, watery droplet, seen chiefly in the morning

Almost 50 per cent of the patients complained of dysuria In 25 per cent it was mild and present chiefly when the patient first voided in the morning In 24 5 per cent it was rather severe and present throughout the day It was usually worse at the onset of the disease, becoming less or disappearing when the discharge lost its gross purulent character Dysuria, however, proved to be a misleading symptom, since it was often present in recently exposed individuals who had no other evidence of the disease, and was frequently absent in severe posterior urethritis

Gross pyuria was observed in every patient This varied at the onset from a clear first glass filled with fine, spiral shreds, to a grossly cloudy first glass containing uncountable large, fluffy

TABLE I

SYMPTOMS AND SIGNS IN 588 NON-GONOCOCCAL URETHRAL INFECTIONS

Symptoms	No of Cases	Per cent
Discharge	572	97 2
Dysuria	291	49 5
Mild	147	25 0
Severe	144	24 5
Urethral itching	21	—
Haematuria	17	—
Frequency	15	—
Painful erections	12	—
Perineal soreness	11	—
Urgency	9	—
Suprapubic pain	7	—
Nocturia	6	—
Pain in scrotum	5	—
Backache	5	—
Pain in groin	3	—
Difficulty in voiding	2	—
Signs		
Gross pyuria	555	94 4
Discharge total	377	64 1
Profuse and purulent	117	19 9
Profuse and watery or muco-purulent	61	10 4
Purulent droplet discharge	134	22 8
Watery droplet discharge	221	37 6
Haematuria total	17	—
Gross admixed	2	—
Profuse terminal	2	—
Droplet terminal	11	—

TABLE II

ENDOSCOPIC FINDINGS IN 51 CASES OF NON GONOCOCCAL URETHRITIS

Clinical Diagnosis	No of Cases	Pendulous Urethra Only	To Urogenital Diaphragm	Intramembranous Urethra	Prostatic Urethra	Bladder
Acute anterior urethritis	14	(12) Desquam exudate Superficial involvement of mucosa	(2) Same	0	0	0
Chronic anterior urethritis	12	(12) Same as above but with occasional granulations	(12) Same	0	0	0
Acute posterior urethritis	13	(6) Severe mucosal reaction when involved	(6) Same	(13) Very intense reaction with hyperaemia ulceration and bleeding	(13) Marked congestion and bleeding	(4) Intense haemorrhagic cystitis
Chronic posterior urethritis	12	(12) Milder reaction more granulations than above	(12) Same	(12) Same with friable bleeding mucosa	(12) Milder congestion but bleeds	0

purulent flocculeS The intensity of the gross pyuria almost always varied with the severity of the discharge Even in the most intense posterior urethritis, however, the second glass was never as cloudy as the first, and the gross pyuria was rarely observed in the other glasses Close observation of the fluctuations of the gross pyuria at subsequent visits proved to be the most reliable means of evaluating the patient's progress

The other symptoms and signs were neither statistically nor clinically significant

Endoscopic Findings (Table II)—During the active phases of the disease 51 patients were cystourethroscoped The clinical impression, based solely on the multi-glass urine test, was confirmed in all instances An adequate and graphic description of the endoscopic findings is given by Harkness (1950a) Cystoscopy was very poorly tolerated

After being cured of their disease 139 patients were cystoscoped Those who responded promptly had no evidence of urethritis, but protracted cases occasionally demonstrated fine mucosal scars in the pendulous urethra

Bacteriological Findings—Altogether 1,390 cultures were taken from 574 patients, 1,794 organisms were isolated in 1,229 cultures, while 161 cultures were sterile (11 5 per cent) *Micrococcus pyogenes* was by far the most common organism isolated There was no correlation between the organisms isolated and the clinical character of the disease

Sensitivity Studies (Table III)—Chloramphenicol exhibited the widest *in vitro* sensitivity range, aureomycin the narrowest

Complications—28 patients were admitted with a posterior urethritis and concomitant prostatitis, sixteen more developed it during the course of treatment Once the disease was presumptively cured, there was no evidence of prostatitis, this was observed in 41 of the 44 patients with a posterior urethritis, the other three failed to return for a final evaluation

No other complications were observed

Sequelae—One patient developed a stricture 8 months after initial infection No other sequelae were seen

TABLE III

IN VITRO SENSITIVITY TO FIVE ANTIBIOTICS OF THE 1 794 ISOLATES FROM 1 390 CULTURES IN 574 CASES OF NON GONOCOCCAL VENEREAL URETHRITIS

Organism	Number of Patients with Organisms Sensitive to				
	Penicillin	Streptomycin	Chloramphenicol	Aureomycin	Terramycin
Micrococcus pyogenes	762	964	1 097	700	794
Beta Streptococcus	81	69	115	81	97
Gamma Streptococcus	71	83	100	82	85
Diphtheroids	73	86	92	62	76
Coliform Bacilli	3	18	20	7	12
AlphaStreptococcus	17	8	23	22	25
Gaffky and Sarcina	15	15	15	12	12
Haemophilus	13	13	18	14	14
Non pathogenic Neisseria	10	11	12	11	14
Aerobic Spore forming Bacteria	5	10	9	8	10
Proteus and Pseudomonas	4	9	6	4	8
Total	1 054	1 286	1 507	1 003	1 147
Percentage	58 8	71 7	84 0	55 9	63 9

Diagnostic Criteria—The following diagnostic criteria for non-gonococcal venereal urethritis can be established

(1) *Presence of a gross pyuria*,
(2) Presence or recent history of urethral discharge

(3) Absence of any of the pathogens (enumerated in the original definition of the disease) in the urethral discharge,

(4) History of previous sexual exposure

Diagnostic Error—The two most common sources of diagnostic error were failure to look for a gross pyuria and giving too much importance to smears It was observed that if the discharge resembled that of gonorrhoea, and organisms morphologically like *N gonorrhoea* were found abundantly in the smear, then a presumptive diagnosis of gonorrhoea was feasible On the other hand, a scanty atypical discharge containing a few Gram-negative cocci should not be labelled gonorrhoea too hastily If there were reasonable doubts a culture was indicated

Exciting Factors—The roles of intoxication, unusual forms of coitus, the menstrual status of partners, and the use of contraceptive jellies by contacts could not be evaluated, because the data were either scanty or too untrustworthy

Prophylaxis—The efficacy of the common prophylactic measures was too difficult to determine because no estimate of the incidence of the disease per modality could be made However, 524 patients gave accurate information of the prophylaxis they used, or did not use, 302 patients used nothing, 91 condoms, 99 "pro kits", and 32 both condoms and "pro kits" Clinically, the disease seen following the use of a "pro kit" was indistinguishable from the others, the organisms isolated were identical in distribution, but there was a difference in the incidence of concurrent gonorrhoea Those who used no prophylaxis had a 19 5 per cent incidence of concurrent gonorrhoea, those who wore condoms a 4 per cent incidence, those who used "pro kits" a 22 2 per cent incidence, and those who used both a 9 4 per cent incidence

Therapy

Of the 588 cases of non-gonococcal venereal urethritis studied, the effectiveness of therapy was fully evaluated in 440 Almost all of those considered to be well were followed for an additional month after being declared cured, half for 3 to 6 months, and a quarter from 6 months to a year Nine of the patients were under treatment from 4 to 7 months One patient, treated for 7 months was still infected 6 months after completing therapy and was considered a therapeutic failure The other 439 patients, both those treated and the controls were discharged as cured

Altogether 113 controls were initially observed for 8 weeks without treatment, seven of whom failed to cooperate In 62 of the remaining 106 (58 5 per cent), the disease subsided spontaneously in a characteristic manner there was a gradual disappearance of all signs and symptoms, and no relapses Of the 44 failures eighteen had induced relapses which followed apparent remissions Eleven patients with acute urethritis in the control group had previously been given penicillin for their concurrent gonorrhoea Ten of these were well in 8 weeks Nine of the control patients had abacterial infections, and only two of these were well at the end of the period of observation, serial cultures having been done weekly for as long as 4 weeks

Specific Therapy—464 patients, including the 44 patients in the control group in whom the disease failed to subside spontaneously, were treated with one or more courses of an antibiotic Of these, 377 were cured, one was not, and 86 failed to meet the criteria for cure and could not be evaluated 251 patients (66 4 per cent) were cured by the first course of medication 43 of these had abacterial infections (97 7 per cent of 44), and the remaining 208 (62 3 per cent) bacterial infections These 251 cases were observed over an average of 4 weeks and 3 days The 126 bacterial infections not cured by one course required 3 4 courses of medication, and were under continuous observation for an average of 10 weeks and 5 days before a final assessment was made

The response, when antibiotics were effective, was an abrupt cessation of all signs and symptoms without relapse The 126 patients who required more than one course of treatment suffered ninety relapses, the majority of which were induced

Penicillin was prescribed 148 times and fully evaluated in 129 patients Its cure rate was 41 9 per cent, far below that of the controls No side-reactions were encountered, but the drug was not prescribed for patients with a history of sensitivity to penicillin

Streptomycin was prescribed 134 times and fully evaluated 119 times, with a cure ratio of 47 1 per cent, considerably below that of the controls One patient developed urticaria, chills, fever, and generalized malaise after receiving 1 5 g of the drug

Chloramphenicol was prescribed 69 times in the bacterial infections, and evaluated 61 times It cured 57 4 per cent of the infections, a rate approximately that of the controls

It was given 57 times to patients with abacterial infections and evaluated 45 times By the first course of medication 43 patients were cured, and there was one failure who was given a second course of the drug and cured, so that the cure rate was 100 per cent Only two out of nine abacterial cases (22 2 per cent) in the control group were cured spontaneously

One patient developed an asymptomatic agranulocytosis after 10 5 g chloramphenicol His white cell count

dropped from 6,100 to 2,900, but returned to normal in 3 weeks

Aureomycin cured 79 4 per cent of 180 patients, this being considerably better than the spontaneous cure rate

Terramycin cured 70 2 per cent of 64 patients, this, too, being significantly better than the spontaneous cure rate

Terramycin and aureomycin produced no untoward side-effects of sufficient severity to cause these drugs to be stopped

Other Regimes or Factors and Therapeutic Measures — The sulphonamides and local measures were not evaluated *per se* Coffee, tea, carbonated beverages, and condiments apparently exercised *no significant influence* on the course of the disease

Role of Previous Treatment —Analysis revealed that treatment given before the patient was referred to the 141st General Hospital played an important role in the promptness with which he responded to treatment The 464 patients treated with antibiotics were divided into six groups

(1) and (4), the acute and chronic cases admitted without prior treatment ,

(2) and (5), the acute and chronic cases previously treated only for concurrent gonorrhoea

(3) and (6), the acute and chronic cases previously treated for non-gonococcal infections

The acute cases previously treated for non-gonococcal infections had received either short courses of penicillin (300,000 to 1,800,000 units), or penicillin in conjunction with 2 or 3 g of one of the other antibiotics In the chronic group, treatment ranged from repeated short courses of assorted antibiotics to antibiotics in conjunction with sounds, prostatic massage, and urethral meatotomy This group had been previously treated for an average of over 3 months

Inadequate, empiric, miscellaneous treatment apparently tended to prolong markedly the course of the disease The variation in relapse rates was equally significant The relapse rate in the acute, previously untreated group (184 patients, 28 relapses) was only 15 2 per cent , while it was 55 6 per cent in the acute, previously treated group , in the chronic, previously untreated group, there were only two relapses in eighty patients (2 5 per cent), while the chronic, previously treated patients suffered 38 relapses in 98 infections (38 8 per cent)

A total of 126 relapses were seen, 75 per cent induced by either liquor or urethral trauma (sounds, cystoscopy) Over half occurred within 2 weeks of completion of treatment, but one did not appear until the middle of the sixth week Spontaneous relapses developed gradually, and usually consisted of a gross pyuria, some dysuria, and a morning droplet discharge Induced relapses occurred more abruptly, almost invariably within 24 hrs of the trauma, and were more severe, the discharge often staining the underclothes through the day

Re-infections —The reappearance of a profuse and purulent discharge was always viewed with suspicion , in fact it was considered almost *prima facie* evidence of re-infection, particularly if the patient had already satisfied the criteria for cure 21 re-infections occurred before the patients had been deemed well, all accompanied by a fresh, concurrent gonorrhoea , 38 occurred from 1 week to 3 months after a presumptive cure had been achieved Invariably patients attempted to conceal their derelictions, to persuade the examiner that they were suffering from a relapse This evasion has given non-gonococcal urethritis the reputation of being more refractory than in fact it is

DISCUSSION

The clinical picture presented here does not differ substantially from that described by observers since World War II (Harkness, 1950a, b, Weil and Harris, 1953 , Willcox, 1949 , King, 1950 , Crouch, Reese, and Boudreau, 1953 , Baier, 1949, Abbott, 1950)

Three significant points however must be made

(1) In approximately three out of five cases the disease will subside spontaneously in 8 weeks ,

(2) The incubation period is virtually identical with that of gonorrhoea (as a corollary, it is highly probable that both diseases are contracted simultaneously, the more virulent gonorrhoea masking the non gonococcal urethritis) ,

(3) The concurrent gonorrhoea rate in this series was only 17 2 per cent , Baier (1949) found it to be 46 per cent in Japan in 1947–48 which can probably be attributed to the later availability of penicillin to Japanese civilians

The importance of the multi-glass urine test has been emphasized , and this has been substantiated by others (Harkness, 1950a , Garvin, 1950, Willcox, 1949 , King, 1950)

Aetiology —This study sheds little light on the possible cause of the disease in at least one third of the instances studied here There can be no question that chloramphenicol attacked a specific entity in the amicrobic infections Since 62 3 per cent of 334 " bacterial ' infections were cured by one course of therapy, the drug being chosen after *in vitro* sensitivity studies, the probability that a specific agent was attacked must be seriously considered In only 49 1 per cent of the controls did the disease subside spontaneously in 4 weeks a period approximately equivalent to the admini

stration of one course of medication On the other hand, 126 other "bacterial" infections did not exhibit this specificity It should, however, be pointed out that 55 of this group of 126 were individuals who had previously been inadequately treated elsewhere The possibility, nevertheless, that a third, as yet unidentified, agent was operative in 71 infections and that this agent is not susceptible to the drugs investigated, must be considered

The source of the infection and the *modus operandi* by which it is disseminated remains unsettled Herman (1938) suggested the possibility that the disease was auto-infectious, and presented evidence to support this Although the condom proved to be an effective barrier to gonococcal infections, it offered no impediment to the invasion of agents causing non-gonococcal urethritis Furthermore, there seems to be no analogous disease in the female In addition, Helmholz (1950) has demonstrated that the male urethra is the habitat of saprophytes as high as the sixth centimetre segment, enhancing the possibility of auto-infection in some instances

Specific Therapy —This study confirmed previous experiences that penicillin (Graham, 1952 , Babione and Graham, 1952 , Willcox, 1953) and streptomycin (Willcox, 1953 , Crouch and others, 1953) are valueless Reports on both chloramphenicol and aureomycin are contradictory (Willcox, 1953 , Crouch and others, 1953), but there is considerable agreement on the value of terramycin (Wagner, Morse, and Kuhns, 1953 , Willcox, 1953 , Ferguson, Miller, and Herrmann, 1952 , Willcox and Findlay, 1952 , Willcox, 1954) Its local use has been recommended by Ferguson and others (1952), but this method of administration has not been studied by others

Local Treatment —While local measures were not investigated in this study, collateral evidence has been presented which suggested that these modalities were not merely of little benefit, but probably detrimental In a like manner, inadequate antibiotic and sulphonamide therapy seemed to prolong the natural course of the disease Willcox (1954) has presented confirmatory evidence of this last observation

Recommended Therapy

(1) Terramycin or aureomycin is the recommended antibiotic in a dosage of 250 mg every 4 hours on a 24-hr basis for 1 week, or a total of 10 5 g

(2) The progress of the disease should be followed by means of the multi-glass urine test

(3) The patient should be asymptomatic and free from gross pyuria for a minimum of 2 weeks before inflicting trauma upon the urethra If there is no relapse following trauma, he is cured

SUMMARY

(1) Out of a total of 1,943 cases of non-gonococcal urethritis, 588 infections in 529 patients were intensively studied 440 patients were fully evaluated in 62 (58 5 per cent) of 106 controls the disease subsided spontaneously in 8 weeks 377 out of 378 (99 7 per cent) were cured by one or more courses of specific antibiotic therapy , of those so cured 43 were abacterial infections, and 334 bacterial 97 7 per cent of the abacterial and 62 3 per cent of the bacterial infections were cured by one course of medication The remaining 126 bacterial infections averaged 3 4 courses of medication and required 2 to 7 months to cure

(2) The probable aetiology of the disease is discussed

(3) A therapeutic regimen is recommended

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URETHRAL STRICTURE IN THE MALE*

A SURVEY OF ONE HUNDRED CASES

BY

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Clinical impressions of the diminution in incidence of urethral stricture in the male are confirmed by the following figures from the Registrar-General's Statistical Review for England and Wales (1951), which show that the number of deaths of males from stricture of the urethra in 1951 was only 38 per cent of that in 1939 These figures, however, reflect not only the diminishing incidence of stricture, but also the beneficial influence of the sulphonamides and antibiotics in reducing the septic complications of stricture during the period under review

Year	Males	Females
1939	304	—
1940	277	—
1941	300	3
1942	293	1
1943	255	1
1944	226	1
1945	195	1
1946	188	3
1947	187	3
1948	170	—
1949	161	3
1950	131	1
1951	117	3

Nevertheless, during the past 5 years over a hundred cases of urethral stricture have been either diagnosed or treated at one male venereal disease clinic One hundred of these cases form the basis of this paper

Age —The percentage of cases falling into 10-year age groups at the time of the first visit is shown in Fig 1 Of the two (2 per cent) under 30 years of age, one had urethritis (gonococcal or non-gonococcal) at the age of 21, and at 26 was admitted to a medical ward with acute retention of urine, after which he failed to attend regularly for dilatation of the stricture, and acute retention recurred on three further occasions (2, 4, and 11 years later). The other was treated elsewhere for gonorrhoea at the age of 23, 5 years before admission to our ward for meatotomy

Ten (10 per cent) cases were over 70 years old, including one of 82 who gave a history of urethritis 60 years previously This patient had, during the preceding 4 years, been regularly instrumented in a surgical ward following temporary suprapubic cystostomy

The mean age on reporting was 53 2 years, with very wide extremes of 82 and 26 Taking account of previous treatment elsewhere, the mean age at the time of diagnosis of stricture was 48 5 years, with a similarly wide range

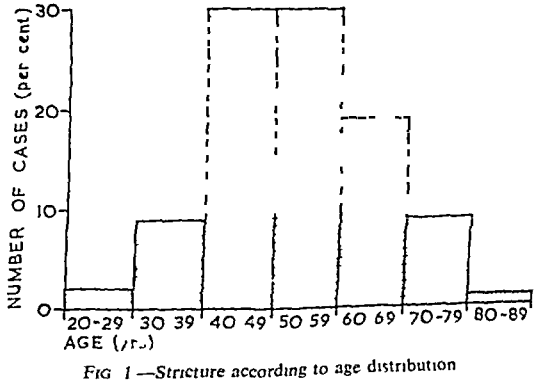

FIG 1 —Stricture according to age distribution

Marital State —69 per cent were either married or widowers A comparable group of non-stricture cases with an average age of 55 years contained 83 per cent of married men, whilst a survey of non-stricture cases all over the age of 20 revealed 58 4 per cent to be married

Number of Strictures per Case —In the series under discussion the diagnosis was made clinically by the passage of sounds Of the strictures thus

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encountered 69 were single, 26 multiple, 2 of the tunnel variety, and 3 could not be classified with certainty Some of those classified as multiple may have been due to "flaps" or "soft-infiltrations" and might not be demonstrable at necropsy In a small proportion normal prostatic hypertrophy may have imparted a sense of obstruction to the sound and may have led to over-diagnosis of posterior strictures

Hunter (1818) has described a case with six separate strictures, and in France cases with between seven and eleven have been recorded Apart from the ribbon or tunnel type, it is rare to encounter more than three separate strictures in an individual case, in the present series two cases exhibited three strictures each, none had more than three

Case Reports

A 3422, aged 48, complaining of a poor urinary stream, gave a history of urethritis 27 years ago and of instrumentation 24 years ago because of difficulty in urination On examination he was found to have strictures at the external meatus, in the anterior urethra 1 in from the meatus, and in the posterior urethra During the first 5 years of attendance at the clinic he required dilatation 28, 20, 21, 20, and 14 times per annum A local anaesthetic was occasionally employed in his case, but pre-medication with analgesics or anti-spasmodics was not needed On two occasions he developed acute urinary retention, the first having been provoked by an alcoholic bout, on each occasion the retention was relieved by passing a metal catheter

E 1522, aged 68, was admitted with acute urinary retention preceded by difficulty and pain on micturition He had also a perineal peri-urethral abscess with a fistula on the posterior surface of the scrotum The acute retention was relieved by suprapubic puncture, and subsequent instrumentation revealed strictures in the anterior urethra, in the bulb, and at the bladder neck Dilatation was repeated on three occasions using morphine pre-medication and a local anaesthetic, after which he defaulted for 3 years He returned with another peri urethral abscess and the strictures were again dilated on three occasions After a further default period of 2 years he was re-admitted with acute retention, which was relieved by suprapubic puncture One month later he developed a further perineal abscess, and was subsequently transferred to an institution

It seems possible that urethroscopy and urethrography might with advantage be more frequently employed in the localization of stricture and in assessing the number of strictures, in the present series the former was only occasionally employed and the latter once Loughnane (1941), in a plea for the more widespread use of urethroscopy and urethrography in the investigation of stricture, refers to the latter method as "a valuable aid too seldom used" He points out that by its use one is enabled to recognize the type of stricture (*i e*, whether annular or ribbon), the number, and the presence or absence of false passages

Site of Strictures—Clinical assessment of the sites of all strictures found (many being multiple) gave the results listed in Table I and illustrated semi-diagrammatically in Fig 2 This supports the common belief that stricture most frequently develops in the bulbar portion of the urethra Reasons put forward in the past to account for this include the looser attachment of the mucosa in this area to subjacent structures, poorer drainage, and damage by injudicious instrumentation At least forty (40 per cent) cases had previously undergone instrumentation at some time but the significance of this is difficult to evaluate, since instruments were formerly used as a routine test of cure Also many patients may have been instrumented at the time of first onset of stricture symptoms and may then have defaulted

Excluding the membranous urethra and bladder neck, 19 2 per cent of all strictures were found to be

TABLE I
CLASSIFICATION OF STRICTURES ACCORDING TO SITE

Site of Strictures	Number of Strictures	Per cent
Meatus	7	5 6
Anterior	19	15 2
Bulb	58	46 4
Membranous	10	8 0
Posterior	24	19 2
Bladder neck	7	5 6
Total	125	100

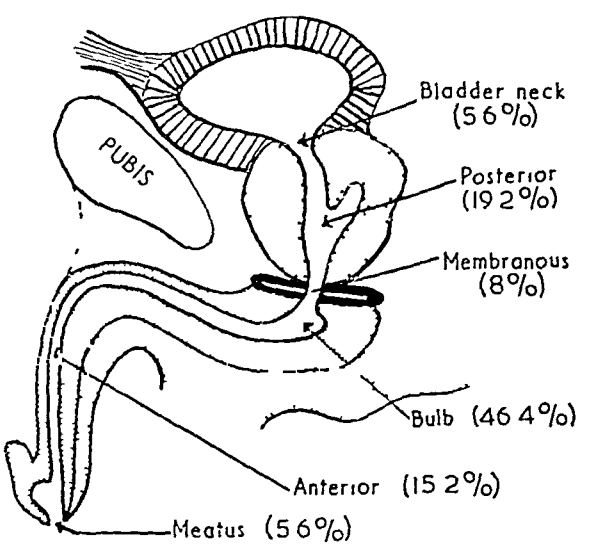

FIG 2—Frequency of anatomical site of strictures

situated in the posterior urethra in this respect our experience is in direct conflict with the prevalent opinion that posterior stricture is rare Thus Loughnane (1941) stated that there were no recorded instances of stricture of the prostatic urethra, and this belief is frequently encountered in the literature

Obstruction at the neck of the bladder constituted a further 5 6 per cent of strictures This well-recognized urological condition is a result of fibrosis extending from the prostate gland and follows previous prostatitis It is frequently associated with stricture formation elsewhere in the urethra and with chronic urinary infection, and will be referred to later

Symptoms —The symptoms complained of by patients on their first visit to the clinic are illustrated graphically in Fig 3 These figures emphasize the importance of the two major symptoms, difficulty and frequency of micturition, and serve as a reminder that a urethral stricture may occasionally present as an intractable mild non-specific urethritis with urethral discharge and evidence of pyuria In these cases treatment of the urethritis is likely to be ineffectual unless the stricture is first found and dilated

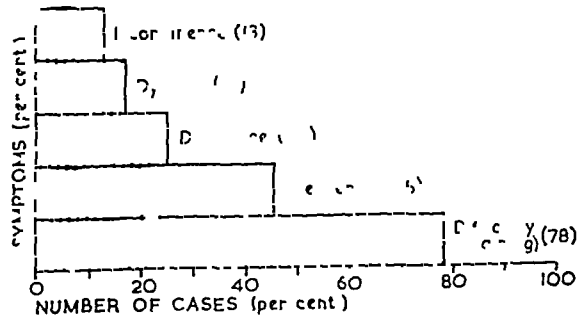

FIG 3 —Symptoms of stricture

A stricture may, none the less, be asymptomatic and bougies should be passed in any case in which suspicion arises, particularly in the age group 40 to 60 years with a history of previous urethritis They should also be passed as a routine after the first attack of acute urinary retention, even in those cases in which relief is achieved without resort to catheterization

In twenty cases (20 per cent) it was possible to estimate the duration of symptoms in patients who had not previously been instrumented The mean period was 37 months, with extremes of 2 weeks and 16 years Half the patients reported within 1 year of onset and seventeen (85 per cent) within 5 years (Fig 4) There is no doubt that many are prepared to tolerate the symptoms listed above,

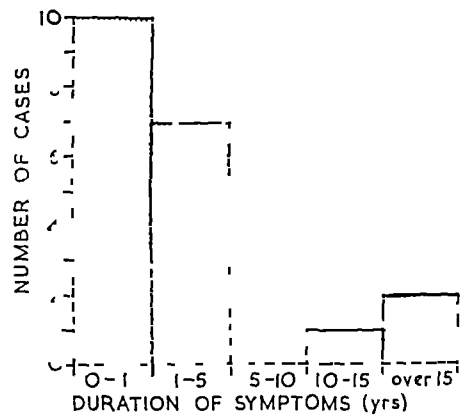

FIG 4 —Duration of symptoms

but they are driven sooner or later to seek advice by the onset of an acute urinary infection or acute retention of urine Thus 41 patients (41 per cent) reported for the first time with acute retention

Acute Retention —This developed in 51 patients (51 per cent) at some stage of their management 32 on one occasion only, twelve on two occasions, five on three, one on four, and one on five occasions, making a total of eighty episodes of acute retention

It is said that exposure to cold, the onset of acute urinary infection, or over-indulgence in alcohol may precipitate acute retention A definite history of alcoholic excess was obtained in only five cases, although it seems likely that its influence is in fact greater in the hospital clinic class of patients constituting this series It is traditional to anticipate a few cases of acute retention around the Christmas and New Year seasons indeed the advice tendered by Buchan (1800) still holds good He wrote

> Persons subject to suppression of urine ought to live very temperate Their diet should be light and their liquor diluting They should avoid all acids and austere wines, should take sufficient exercise lie hard, and avoid study and sedentary occupations

Simple measures such as sedation (morphine or pethidine), antispasmodics (Trasentin suppositories), hot hip-baths, and/or urethral catheterization sufficed to relieve retention in 49 cases out of eighty (61 per cent) Suprapubic puncture by hollow needle or small trocar and cannula was required in twenty cases (25 per cent) In eleven (14 per cent) suprapubic catheterization (cystostomy) was performed of these eleven cases the cystostomy was temporary in eight (Table II, opposite)

TABLE II
RELIEF OF ACUTE RETENTION

Means of Relief	Cases	Per cent
Simple measures and/or urethral catheterization	49	61
Suprapubic puncture	20	25
Suprapubic catheterization temporary	8	10
Suprapubic catheterization permanent	3	4
Total	80	100

Urinary Infection—The sequence of obstruction, stasis, and infection is well recognized in urology accordingly it is not surprising that 66 cases (66 per cent) exhibited some degree of urinary infection, varying from mild chronic urethritis to acute cystitis In most cases the infection remained chronic with periodic exacerbations, and was best controlled by regular dilatation of the stricture combined with frequent urine culture and appropriate chemotherapy or antibiotics (Fig 5 and Table III)

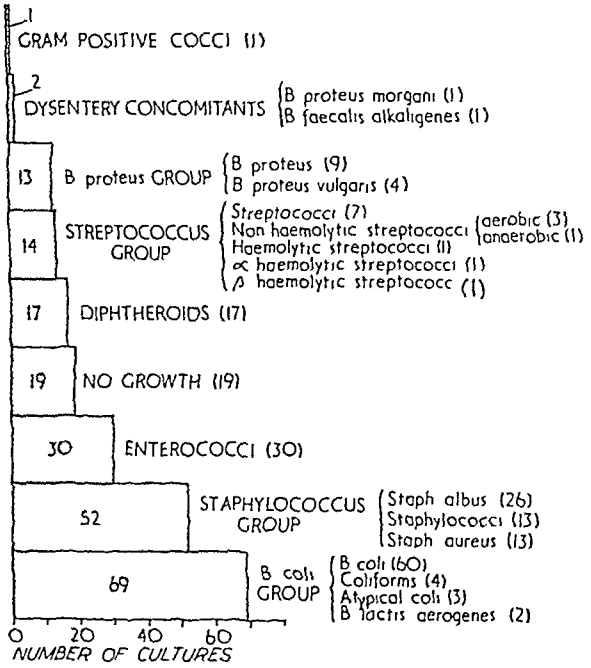

FIG 5.—Results of cultural examination of 143 specimens of urine from 58 cases

TABLE III
RESULTS OF 143 URINE CULTURES FROM 58 CASES

Organism	No of Cultures	Organism	No of Cultures
B Coli	60	Atypical *B Coli*	3
Enterococci	30	*B Lactis Aerogenes*	2
Staph Albus	26	Gram positive cocci	1
No growth	19	Haemolytic streptococci	1
Diphtheroids	17	*B Faecalis Alkaligenes*	1
Staphylococci	13	*B Proteus Morgani*	1
Staph Aureus	13	Non haemolytic streptococci (anaerobic)	1
B Proteus	9	α Haemolytic streptococci	1
Streptococci	7	β haemolytic streptococci	1
Coliforms	4		
B Proteus Vulgaris	4		
Non haemolytic streptococci	3		

Previous Urethritis—A history of previous urethral discharge was given by 74 patients (74 per cent), which must be taken to include gonorrhoea and non-gonococcal urethritis although the relative importance of each cannot be estimated Of these, 42 (42 per cent) stated that they had previously had gonorrhoea the remaining 32 (32 per cent) may have had either gonorrhoea or non-gonococcal urethritis

Of the 74 patients who had had previous urethral discharge, 44 had never previously had instruments passed, whilst thirty had been instrumented at some time in the past, presumably either for obstructive symptoms or merely as a test of cure

Time Necessary for Development of Symptoms—The mean period from infection to development of stricture symptoms, so far as could be ascertained in 26 cases of previous gonorrhoea, was 20 9 years, with a very wide range giving extremes of 4 years and 35 years In seventeen cases of previous urethritis (nature unknown) the mean period was 21 3 years, with extremes of 1 year and 42 years The close similarity of these figures suggests that either there is no difference in the time of development of strictures following gonorrhoea and non-gonococcal urethritis, or that most of the cases listed as having had "urethritis of unknown aetiology" had in fact suffered from gonorrhoea (or a mixed gonococcal and non-gonococcal infection) at that time

In both groups the greatest number of cases developed symptoms in the period from 10 to 34 years after the time of infection (Table IV), and if the two groups are combined it will be seen that 34 cases out of 43 (79 1 per cent) developed in this period

TABLE IV
PERIOD FROM INFECTION TO DEVELOPMENT OF SYMPTOMS

Years	Gonorrhoea	Urethritis ? Gonococcal + Non Gonococcal Urethritis	Total
0–4	1	2	3
5–9	1	1	2
10–14	6	4	10
15–19	3	1	4
20–24	4	1	5
25–29	6	1	7
30–34	4	4	8
35–39	1	1	2
40–44	0	2	2
	26	17	43

This is in general agreement with the following figures quoted by Swinney (1952) in 66 per cent of strictures symptoms take 15 years or longer to develop, and only 5 per cent experience symptoms within 5 years Similarly Beard and Goodyear (1948) consider that in the majority of cases symptoms do not arise for 20 years or more

Factors in Causation—It is frequently said that the trauma of repeated irrigation or ill-judged instrumentation is more often responsible for stricture formation than is urethritis The facts that in this series 74 patients (74 per cent) admitted previous urethritis, whereas only twenty (20 per cent) gave a definite history of having been treated by irrigations in the past, and only forty (40 per cent) had previously had bougies passed, suggest that stricture may in fact occur more commonly in those who remain untreated for their original urethritis or who default before they are proved cured

Be this as it may, analysis of the past histories in respect of each of these two features certainly fails to support the suggestion that either irrigation or instrumentation, as normally used for therapeutic purposes, played any significant part in the aetiology of urethral strictures in this series

Thirteen patients (13 per cent) gave no history of urethritis, irrigation, or instrumentation at any time previously In these cases the cause remains obscure although it is highly probable that their memories were at fault Analysis of these thirteen cases reveals a total of sixteen separate strictures, three having stenosis at two sites (Table V) The percentage distribution according to site resembles that found in the overall series, except that no strictures were encountered at the meatus or in the prostatic urethra The absence of meatal strictures in this small group and the preponderance of strictures in the bulbar urethra combine to eliminate congenital defect as a likely cause of the urethral stenosis in these cases, and suggest that the same causes were operative here as in the complete series, despite the negative histories

TABLE V

SITE NUMBER AND PERCENTAGE OF STRICTURES IN CASES WITH NO HISTORY OF URETHRITIS IRRIGATION OR INSTRUMENTATION

Site	Number	Per cent
Anterior	3	18 7
Bulb	10	62 5
Membranous	1	6 3
Bladder Neck	2	12 5
Total	16	100

Frequency of Dilatation (Table VI)

Of the one hundred cases under study, a diminishing number of patients returned annually over a period of 5 years for regular dilatation of their strictures The 5-year period was arbitrarily chosen, and the mean figure of dilatations per patient was calculated The results show that in the first year of attendance the mean number of dilatations per patient was 5 9, in the second year, 4 7, and

TABLE VI

MEAN NUMBER OF DILATATIONS PER PATIENT PER YEAR

Year	Number Attending	Mean Dilatations
1	97	5 9
2	53	4 7
3	45	4 9
4	39	4 6
5	34	4 6

in the succeeding years, 4 9, 4 6, and 4 6 respectively (*i e*, the figure remains constant) Probably in no other condition is a higher degree of individual attention necessary, and it is not justifiable to argue from the general to the particular case It can be assumed, however, that for every regularly attending stricture patient on the clinic records, an average of between four and five attendances for dilatation will be necessary each year For this reason it would seem desirable that all newly-diagnosed stricture patients should be impressed with the fact that good health requires regular attendance at least every three months (quarterly), and that "cure" in the accepted sense is impossible to attain Loughnane (1941) reminds us that the century-old belief that "the bougie must be a lifelong friend of a stricture patient" still holds good, and asserts that the maximum period between dilatations should in no case exceed 6 months

With these general rules we are in complete agreement, but it is nevertheless true that wide variations exist in the frequency with which individual patients require to undergo instrumentation This is well shown in Table VII These figures emphasize the fact that each case constitutes an individual therapeutic problem

TABLE VII

EXTREMES IN FREQUENCY OF DILATATION REQUIRED BY INDIVIDUALS IN SUCCESSIVE YEARS

Year	Maximum	Minimum
1	41	1
2	25	1
3	21	1
4	20	1
5	14	1

The annual diminution in the numbers attending in successive years after the diagnosis of stricture has first been made (Table VI) can be accounted for by

(i) Those who believe themselves cured *i e*, whose symptoms are sufficiently relieved for an indefinite period In this connexion it is of interest that Harkness (1950) states that congenital strictures may, on rare occasions, occur in the anterior and posterior urethra in addition to their more frequent occurrence at the meatus Such strictures, when situated proximal to the meatus, are formed by a single reduplication of mucous membrane only On urethroscopy they appear grey and translucent, and they may be cured by one instrumentation

(ii) Those who " default," *i e*, symptoms present but patients unwilling or unable to resume full attendance

(iii) Those who are transferred to other clinics or hospitals

(iv) Those who leave the district or die

In these cases one hesitates to employ the same defaulter-tracing techniques which work so well in other categories of venereal disease patients, for many are elderly men with grown-up families and it is undesirable to risk disclosing the personal or family skeleton to other relatives Furthermore, many are of an age when death from other or natural causes might occur at any time, and no notification of this may have been received at the clinic

Assuming that the management of the patient runs a smooth course and that he escapes the ever-present hazards of acute retention, acute cystitis (or other suppurative condition of the genito-urinary tract) or intercurrent infection elsewhere, for any of which he may require in-patient treatment, he will normally need urethral instrumentation perhaps five times annually Each such treatment necessitates three out-patient visits

(1) The patient s general condition is assessed, a date is fixed for instrumentation, and prophylactic chemotherapy is started

(2) The instrumentation is carried out, preferably with pre-medication

(3) The patient reports any complications or unpleasant sequelae

Thus on the average each patient might require to attend the out-patient clinic on fifteen occasions each year This is identical with the experience of Kidd (1916) and although the total number of stricture cases may be much fewer to-day, the time expended on the individual patient has remained unchanged

Russell (1915) believed that in spite of surgical progress the treatment of urethral stricture had always lagged behind He classified the available methods as follows

(*a*) *Preventive*—Surely the method of choice and, since the introduction of antibiotics, capable of achievement in most cases

(*b*) *Surgical*—(*i*) Not involving perineal operation, *i e*, simple dilatation and/or internal urethrotomy

(*ii*) Involving perineal operation, *i e*, external urethrotomy or excision of the stricture

His main conclusions were that in cases easily managed by dilatation no further operation is advisable, but that in very difficult or impassable strictures excision of the stricture should be performed

Advances in surgical technique now make it possible to combine excision with plastic reconstruction of the urethra from a buried strip of skin, after the method described by Swinney (1952)

According to Swinney this operation is especially indicated in the following types of stricture

(*a*) the resilient stricture, which contracts down a few days after every dilatation ,

(*b*) the tortuous and difficult stricture in which instrumentation is followed by pain, rigors, and fever ,

(*c*) the stricture associated with fistulae, in which there is extensive peri-urethral and perineal fibrosis

In such cases the more widespread use of this method may make possible a considerable reduction in the frequency of subsequent instrumental dilatation

Coincident Venereal Infections—The presence of post-inflammatory urethral stricture presupposes in most cases exposure to venereal infection at some time in the past It is therefore not surprising to find either history or clinical evidence of other venereal infections in cases investigated for stricture which may be tabulated as follows

History of Syphilis in the past		5
Evidence of Syphilis	latent	8
	early	1
	tabes	1
History of Urethritis (gonococcal and non-gonococcal)		74
Evidence of Gonorrhoea	acute	3
	chronic	2

In the present series, as previously stated, 74 patients gave a definite history of urethral discharge, which must have included both gonococcal and non-gonococcal urethritis Furthermore in five

patients there was evidence of gonococcal infection at the time of reporting because of stricture symptoms three had acute gonorrhoea (purulent urethral discharge and gonococci present in urethral films) following recent exposure to infection, whilst two had evidence of chronic gonococcal infection (slight urethral discharge, threads in the urine, and a strongly positive GCFT)

Five patients had been treated for syphilis in the past, and a further ten were found to have previously undiagnosed syphilis on first reporting One of these had a primary chancre, eight were latent syphilitics, and one had tabes dorsalis Thus at least 15 per cent had been infected with syphilis at some time

Complications and Sequelae to Stricture (Table VIII)

The relatively high incidence of epididymitis, peri-urethral abscess, fistula formation, and prostatic calcification should be noted

Epididymitis may be ascribed to back pressure along the vasa deferentia exerted by a large volume of residual infected urine, intensified by straining during micturition Possibly some cases may be blood-borne or metastatic

Peri-urethral abscess may arise in the course of acute urethritis as a result of blockage of the duct of, and abscess formation in, one of the glands of Littre, or later as the result of maceration or trauma of the urethral mucosa proximal to a stricture It is easy to conceive that the strain of micturition might force out a small quantity of infected urine into the submucosa and thus initiate a focus of suppuration An analysis of this group of septic complications shows that bacteriological examination of the abscess pus was made on eleven occasions in a total of eight patients, one patient having infected hydrocele bilaterally, and the other seven exhibiting peri-urethral abscesses Coliform organisms were isolated on five occasions, non-haemolytic streptococci on three occasions, *Staphylococcus albus* on three, *Enterococcus* on two, and *B proteus*, *Staphylococcus aureus*, and diphtheroids on one occasion each In over two-thirds of cases identical organisms were cultured from the urine

TABLE VIII

COMPLICATIONS AND SEQUELAE

(Occurring in a Total of 41 Cases out of 100 Observed)

Complication	Cases	Remarks
Epididymitis	8	1 case bilateral 1 case two successive attacks
Peri urethral abscess	12	9 perineal 2 scrotal 1 prostatic
Infected hydrocele	1	Bilateral
Fistula	7	4 perineal 3 scrotal
Carcinoma Prostate gland	2	—
Bladder	2	—
Calcification	9	Prostate (+ in one case vesical calculus)
Hernia (inguinal)	2	1 bilateral
Haemorrhoids	1	Prolapsed
Prostatic hypertrophy	2	—
Diverticula	1	Bladder
Hydronephrosis	1	Right side
Peri nephric abscess	1	—
Renal failure	1	—
Other conditions	2	1 verruca of glans 1 bladder papilloma

Prostatic calcification occurred in nine cases and was usually not productive of symptoms It has been suggested that the normal corpora amylacea may form the nuclei of phosphatic stones, especially in the presence of long-standing chronic urinary infection associated with urea-splitting organisms (*e g*, *B proteus*, *B pyocyaneus*) and a highly alkaline urine Other cases represent quiescent and calcified tuberculous foci in the gland, and in these there is a small but present risk of causing acute miliary tuberculosis as the result of surgical interference

In non-tuberculous prostatic calcification, such as that occurring in association with long-established urethral stricture, the diagnosis is made by the presence of one or more of the following signs

(*a*) a hard mass in a mobile gland on rectal examination,

(*b*) crepitus elicited on rectal examination,

(*c*) 'grating' sensation during the passage of metal bougies

(*d*) characteristic x-ray appearances

In eight of the cases the diagnosis was established by x-ray examination and in the ninth the condition was recognized during cystoscopy In the differential diagnosis it is important to bear in mind carcinoma of the prostate and (as previously mentioned) calcified tuberculosis Differentiation from carcinoma of the prostrate is aided by the findings on rectal examination (? fixity), the serum acid phosphatase, radiological examination for evidence of bone metastases, and the results of punch biopsy (Semple, 1951), and from calcified tuberculosis by the history and presence of clinical or radiological evidence of tuberculous foci elsewhere for example, lungs, kidney

Winsbury-White (1948) states, and our experience confirms, that if the stones are small or few in number symptoms are non-existent and no treatment is called for, if they are large or numerous, and especially if associated with obstruction and sepsis, any of the following symptoms may be caused frequency of micturition dysuria, perineal discomfort or pain, pyuria, slight terminal haematuria When symptoms arise, treatment is by prostatectomy

A frequent sequel to urethral stricture and chronic urinary infection is the condition known as " small fibrous prostate " (*prostatisme sans prostate*), in which there are symptoms of prostatic obstruction but no enlargement of the gland is found on palpation The essential lesion is a thickening of the posterior lip of the internal meatus by an extension of dense fibrous tissue from the primary focus of sclerosis in the prostate gland The condition results from previous prostatitis On rectal examination the prostate feels normal in size or smaller than normal, but it is sometimes indurated and tender Prostatic massage and microscopic examination of the expressed fluid reveal pus cells On cystoscopy residual urine, trabeculation, hypertrophy of the median bar, sacculation, and chronic cystitis are found Minor degrees may be treated by dilatation using large metal bougies (after preliminary meatotomy if necessary), prostatic massage, and posterior irrigations If symptoms continue, either transurethral resection or open dissection is indicated, followed by subsequent bouginage (Walker, 1948) It has been stated previously that 5 4 per cent of all strictures encountered in this series took this form of stenosis at the bladder neck

Of the remaining sequelae listed in Table VIII, inguinal hernia, prolapsed haemorrhoids, vesical diverticula, hydronephrosis, may all be attributed to back pressure behind a stricture of long duration, although they might equally well be adventitious

Summary

An analysis of one hundred cases of urethral stricture is made according to anatomical site and symptomatology

It emerges that stricture of the posterior urethra (exclusive of the membranous urethra) is by no means rare, though frequently stated to be so If obstruction at the bladder neck is included, 24 8 per cent of all strictures in this series were posterior

An account is given of the complications and sequelae occurring in this series during a limited period of observation

I wish to thank Dr Robert Lees for permission to publish this article

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ANTICOMPLEMENTARY REACTIONS IN SYPHILIS*

BY

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In his recent article Lighter (1953) demonstrated that sera from patients suffering from congenital syphilis were responsible for anticomplementary reactions about seven times more often than would be expected were anticomplementary reactions distributed evenly among sera from patients with congenital syphilis and those with acquired syphilis

A similar observation has also been made in our laboratory during the last few years, and this has led us to carry out an investigation of the possible causes of this increased frequency of anticomplementary reactions in sera from patients with congenital syphilis

In the original observation it was noted that a number of anticomplementary sera also reacted with a syphilis flocculation test Out of a total of 393 sera from patients diagnosed as suffering from syphilis, 36 were anticomplementary These sera were tested by a modified Kolmer complement-fixation test (Rappaport and Stark, 1953) and also by the following flocculation tests Kahn, Meinicke, Rapid T (Rappaport and Eichhorn, 1950), and cardiolipin (Rappaport and Eichhorn, 1951) Of the 36 anticomplementary sera, fourteen were found to react positively with all four flocculation tests, twelve with three of these tests, seven with two of the tests, and three with one test Most of the positive sera were detected by the Rapid T method (Table) Some of these " anticomplementary " sera proved to be from patients suffering from primary untreated syphilis or congenital syphilis

In an attempt to discover the reason of the anti-complementary reactions the following experiment was set up various syphilitic sera were tested by a modified Kolmer complement-fixation test but instead of one control tube of serum with 2 units complement, two tubes were used, the second containing only 1 5 units complement With some sera

TABLE

REACTIVITY OF SYPHILITIC ANTICOMPLEMENTARY SERA BY FOUR FLOCCULATION TESTS

Test				No of Sera
Cardiolipin*	Meinicke	Kahn	Rapid T†	
+	+	+	+	14
+	+	−	+	7
+	−	+	+	5
+	−	−	+	3
−	−	+	+	2
−	+	−	+	1
+	−	+	−	1
−	+	−	−	2
−	−	+	−	1

* Rappaport and Eichhorn (1951)
† —— —— (1950)

the control tube with 2 units complement showed haemolysis while that with 1 5 units showed none In syphilitic sera from patients with no history of recent infection, both control tubes showed haemolysis, indicating that even 1 5 units complement were sufficient for the proper functioning of the haemolytic system In cases in which this smaller quantity of complement was insufficient and no haemolysis occurred in the control tube, one could assume that the complement was either destroyed by the serum or fixed by some component of the serum

The analysis of these cases made it apparent that such anticomplementary reactions in the tube with the smaller dose were associated with recent infections or congenital syphilis It could, therefore, be inferred that the agent which removed the complement in the control tube was actually fixed by syphilitic antigen, or by a substance which behaved serologically like syphilitic antigen, the presence of this antigen in the serum causing it to be anticomplementary

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It is well known that soon after bacterial or viral infections antigen appears in the circulatory system and stimulates the production of antibodies In the carrier state also there is a continuous production of antigen In convalescence the antigen disappears, but the antibodies remain and account for certain serological and immunological reactions

A similar situation may be postulated in syphilis in the acute stage antigen circulates together with antibodies in the blood , when this " acute " serum is mixed in the control tube with a small quantity of complement, the antigen binds it and prevents the subsequent haemolysis of the haemolytic system When more complement is used, enough of it may remain after fixation by the " native " antigen to react in the control haemolytic system In cases of treated or cured syphilis, antigen is no longer present in the blood, and even 1 5 units complement in the serum control tube suffice to produce haemolysis

In sera known to be syphilitic which are at the same time anticomplementary, the amount of circulating antigen is most probably high enough to fix all the complement added to the control tubes This explanation would fit both our data and those presented by Lighter (1953)

The quantities of complement in the control tubes of anticomplementary sera might be so adjusted that there would be enough to fix the " native " antigen and the haemolytic system, while, in the test proper all the complement would be fixed by both the " native " and the added antigen One has to bear in mind, however, that non-syphilitic antigens might be circulating in the blood which would bind complement in the control tube In doubtful cases, therefore, where an anticomplementary reaction is observed, one has to rely on flocculation tests for a serological diagnosis

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FURTHER STUDIES ON THE EFFECT OF SOME ANTI-COAGULANTS UPON SERO-DIAGNOSTIC TESTS FOR SYPHILIS

II HEPARIN, THYMOL-FLUORIDE, ISOTONIC OXALATE, AND CONCENTRATED CITRATE SOLUTION*

BY

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Ample evidence is available that body fluids other than serum contain antibodies (Coleman and Appleman, 1953, Kanter and Appleton, 1940, Klauder and Kolmer, 1921) Occasionally (Biro, 1947) these fluids reveal antibodies more frequently and sooner after infection of the bone marrow in syphilis Plasma also has an antibody content (Addis, 1912, Cowie, 1909, Gurd, 1912), although some anti-coagulants interfere with the measurement of syphilitic reagin However, upon the removal of the fibrinogen, some anti-coagulants have no appreciable effect upon the serologic tests Blood treated with potassium oxalate in optimal concentration can, therefore, be used as well as serum in these tests

The effects of the treatment of blood on the sero-diagnostic tests for syphilis using the following anti-coagulants were studied heparin, thymol-sodium fluoride mixture, an isotonic potassium and ammonium oxalate mixture, and a concentrated sodium citrate solution It was observed that clotted blood often resists haemolysis of the erythrocytes by bacterial lysis, enzymatic action, or physical forces, considerably longer than will a sample of the same blood drawn at the same time and treated with potassium oxalate salts sufficient to prevent coagulation Potassium oxalate, although not added to the blood-taking tubes with sterile technique, will usually be sterile upon bacterial culture, and it is doubtful if the salt itself introduces micro-organisms into the blood

It seems possible that because erythrocytes of oxalated blood are not bound up in a fibrin clot, they present a greater surface for chemical or physical damage, or that the oxalate interferes with the release of some of the antibodies from lymphocytes Either the anti coagulant prevents the normal release from the leucocytes or, in interrupting the clotting mechanism, some step essential for antibody release does not occur

Fleck and Murczynska (1949) reported a phenomenon termed " leukergy " in which citrated blood in disease caused a clumping of leucocytes into homogenous groups Leukergy lasts 4 days, it is more frequent in infectious diseases and it is not directly related to a phagocytosis Other theories are that the lymphocytes secrete antibodies and that leukergy is not just a liberation upon cytolysis (Grabar, 1950), or that the lymphocytes form antibodies (Dougherty, Chase, and White, 1944, 1945, Ehrich and Harris, 1942)

It is important to know whether the plasma titre of reagin antibody is at the same level as the serum titre, and also the effects of the various anti coagulants upon the antibody levels and their measurement

Method

The VDRL slide the standard Kahn and the cardiolipin Mazzini flocculation tests were used Evidence that more than one type of antibody can be identified and measured is plentiful (D Alessandro and Dardanoni 1953 Eagle and Hogan 1940, Rein and Kostant 1949) For this reason the Kolmer complement fixation test was included These sero diagnostic tests were performed as described in the Manual of Serologic

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Tests for Syphilis " (1949) For comparative purposes of the strength of the reactions, the VDRL test was rated in plus signs as in the Mazzini flocculation test

Plasma specimens were prepared with the following anti-coagulants heparin, concentrated sodium citrate, a thymol sodium fluoride mixture (Sander, 1923), and an isotonic mixture of potassium and ammonium oxalate (Heller and Paul, 1934)

The heparin and 0 2 ml of a 25 per cent solution of sodium citrate were contained in a sealed tube, a Vacutainer * This concentrated solution minimized the dilution effects and gave a final concentration of 0 05 g sodium citrate per 5 ml blood Vacutainers with 5 mg thymol and 50 mg sodium fluoride were used To these tubes containing the dried powder were added 5 ml blood, 6 mg powdered ammonium oxalate and 4 mg potassium oxalate were placed likewise in Vacutainers designed for 5 ml blood

Blood specimens were collected in the usual manner from a prominent vein of the arm A portion of the sample was allowed to clot in a clean dry test tube and the remainder was added to the tubes containing the anti-coagulant The plasma was removed after a 5-minute period of centrifugation and then heated for 30 min at 56° C At the conclusion of the sensitization period, each sample was centrifuged for 10 min at 3,000 revolutions per minute The supernatant, thus cleared of precipitated fibrinogen, was decanted into another tube and then employed as a serum would be in the various sero diagnostic tests

Results

The results are summarized in Tables I, II, III, and IV

Using heparin (Table I) it can be seen that the tests on the plasma appear slightly more sensitive This is true in the flocculation tests even excluding all differences of only one plus degree In the series studied there was no loss of specificity and heparin was anticomplementary in the complement-fixation tests Reports that heparin is unsuitable for Wassermann reactions or agglutination tests (Diggs, 1952) must be related to the individual procedures Techniques for the precise titration of complement (Brooks, 1920), measurement of complement fixation in small volumes (Eckert, Reeve, and Beard, 1953), or the refined spectrophotometric standardization of complement for fixation tests (Kent, Bukantz, and Rein, 1946, Mayer, Eaton, and Heidelberger, 1946) undoubtedly could not be successfully performed on plasma treated with heparin Table I reveals that the agreement in the Kolmer test is good in frank high-titre luetic sera as well as in negative cases In the treated Cases 11, 12, 14, and 15, the heparin plasma appears to be anticomplementary The destruction of complement by heparin can be easily demonstrated by reducing the amount of complement in the Kolmer tests At a reduced level in negative tests negative serum Kolmer reactions are obtained, whereas the heparin plasma Kolmer reactions will all be doubtful or weakly positive, indicating that complement has been destroyed by the heparin

Table II shows that sodium citrate tends to make the tests more sensitive This increased

TABLE I

COMPARISON OF RESULTS IN 22 TREATED CASES OF SERUM AND HEPARIN PLASMA

Case No	Serum				Heparin Plasma			
	Kahn	Mazzini	VDRL Slide	Kolmer	Kahn	Mazzini	VDRL Slide	Kolmer
1	4	3	3	444440	4	2	3	444440
2	0	2	2	000000	±	2	3	000000
3	0	3	3	444400	3	3	2	444400
4	0	1	1	000000	3	1	1	000000
5	3	2	2	443300	4	2	1	442000
6	1	1	2	000000	3	3	2	000000
7	1	1	2	000000	0	0	1	000000
8	0	0	0	±00000	0	0	0	000000
9	4	2	2	321000	4	2	2	321000
10	0	0	0	000000	0	0	0	000000
11	0	±	0	110000	0	±	±	300000
12	0	0	0	000000	0	0	0	300000
13	4	3	4	444440	4	3	3	444440
14	2	1	±	000000	2	±	±	300000
15	2	[illegible]	1	000000	3	±	1	310000
16	[illegible]	0	0	000000	1	0	0	±00000
17	0	0	0	000000	±	0	0	100000
18	0	±	0	000000	0	±	0	000000
19	0	±	0	000000	0	1	0	000000
20	4	4	4	000000	4	4	4	000000
21	4	4	3	443000	4	4	3	443000
22	0	±	0	000000	0	1	±	000000

*Vacutainer was supplied by the Becton Dickinson Company Rutherford New Jersey

TABLE II

COMPARISON OF RESULTS IN 28 TREATED CASES OF SERUM AND PLASMA TREATED WITH 0 2 ml 25 PER CENT SODIUM CITRATE (0 05 g /5 ml)

Case No	Serum				Sodium Citrate Plasma			
	Kahn	Mazzini	VDRL Slide	Kolmer	Kahn	Mazzini	VDRL Slide	Kolmer
1	2	±	±	440000	3	3	3	420000
2	0	0	0	000000	0	±	±	000000
3	1	1	1	000000	2	2	2	000000
4	1	±	±	000000	2	2	1	000000
5	4	2	2	443000	3	3	2	430000
6	4	3	4	ISQ*	4	4	3	444300
7	4	4	2	444430	4	4	4	444300
8	4	4	4	443000	4	4	4	441000
9	4	4	3	441000	4	4	4	310000
10	0	±	0	000000	2	1	±	000000
11	3	4	4	444400	3	4	3	444210
12	±	2	2	441000	3	2	2	441000
13	4	4	4	444400	4	4	4	443000
14	1	2	2	000000	2	3	2	000000
15	0	0	0	000000	0	0	0	000000
16	±	±	1	210000	1	1	1	210000
17	2	2	2	AC	2	2	2	AC
18	0	0	±	000000	0	1	±	000000
19	4	1	2	AC	4	3	2	444441
20	2	2	2	000000	1	3	2	000000
21	4	3	3	000000	3	4	3	441000
22	0	0	0	AC	0	0	0	AC
23	±	1	1	000000	1	2	1	410000
24	0	0	±	000000	0	±	±	000000
25	0	±	1	000000	0	1	±	000000
26	4	4	4	444440	4	4	4	444100
27	4	3	2	000000	4	3	2	000000
28	3	3	3	443000	3	3	3	441000

*Insufficient serum for test

sensitivity is seldom rated over one plus degree However, wherever there is a difference in the grading of a plasma and the corresponding serum, it is always the plasma that has reacted more strongly There does not appear to be any unusual distribution between complement-fixation tests and flocculation tests The more concentrated (0 1 g per ml) sodium citrate, which minimizes the dilution effect, does increase the precipitation in the flocculation test This was seen only in treated cases, however , twenty negative cases were uniformly negative Anticomplementary reactions were not increased

TABLE III

COMPARISON OF RESULTS IN 35 TREATED CASES OF SERUM AND PLASMA TREATED WITH THYMOL-FLUORIDE MIXTURE

Case No	Serum				Thymol sodium Fluoride Plasma			
	Kahn	Mazzini	VDRL Slide	Kolmer	Kahn	Mazzini	VDRL Slide	Kolmer
1	0	0	0	000000	0	±	2	000000
2	0	0	1	000000	0	1	2	000000
3	3	3	3	000000	3	3	3	000000
4	±	2	2	000000	1	2	4	000000
5	4	4	4	444300	4	4	4	444100
6	3	3	1	441000	3	4	4	443000
7	0	±	0	±00000	±	2	2	310000
8	±	1	±	000000	±	3	3	000000
9	2	2	2	221000	±	2	3	431000
10	±	2	2	321000	1	2	2	321000
11	±	0	0	000000	±	±	1	000000
12	3	3	1	221000	3	2	2	000000
13	±	±	±	000000	3	1	4	000000
14	4	4	4	444400	4	4	4	444200
15	0	0	0	000000	0	2	2	000000
16	3	2	2	000000	3	3	4	000000
17	3	±	±	444440	4	3	±	444440
18	2	1	1	000000	2	2	4	000000
19	1	3	2	000000	1	3	4	410000
20	2	3	3	000000	3	3	4	410000
21	2	3	1	000000	3	2	4	000000
22	4	±	4	000000	4	4	4	300000
23	0	4	0	000000	4	4	2	000000
24	4	0	1	444430	0	±	1	444410
25	3	2	1	420000	4	1	2	200000
26	4	±	4	444400	3	1	4	444000
27	0	4	0	000000	4	4	±	000000
28	0	0	0	000000	±	0	2	000000
29	±	0	1	100000	0	0	3	100000
30	0	2	0	000000	2	2	±	000000
31	4	0	4	444440	0	0	4	444440
32	±	4	0	000000	4	±	1	000000
33	4	0	2	000000	±	0	3	000000
34	2	2	4	100000	4	2	2	100000
35	0	2	0	000000	2	3	2	000000
		0			0	0		

The results of the treatment of blood with thymol-fluoride mixture are summarized in Table III There is clearly more precipitation in the flocculation procedures The increase in positive plasma reactions using the Kolmer technique (Cases 19, 20, and 22) over similar reactions when using serum would indicate that the anti-coagulant in plasma is anticomplementary In twenty negative cases at least five revealed precipitation in the flocculation tests Four of these represented doubtful tests with the VDRL when using plasma and one was rated at one plus with the Mazzini test when using plasma There is a further disadvantage in the use of this thymol-sodium fluoride mixture as an anti-coagulant Unless the plasma is removed within 24 hrs after the collection of the blood a definite haemolysis occurs, even at icebox temperature (12° C) This in turn makes the flocculation tests more difficult to read It is of interest to note that this anti-coagulant interferes with some enzyme activities It cannot be used in urea nitrogen determinations that depend upon urease (Roe, Irish, and Boyd, 1927) However, this feature is advantageous in glucose determinations (Bowman and Enterline, 1954) It has been shown that sodium fluoride inhibits the enzyme enolase in the glycolytic pathway (Baldwin, 1952)

TABLE IV

COMPARISON OF RESULTS IN 21 TREATED CASES OF SERUM AND ISOTONIC OXALATE PLASMA (HELLER AND PAUL MIXTURE)

Case No	Serum				Isotonic Oxalate Plasma			
	Kahn	Mazzini	VDRL Slide	Kolmer	Kahn	Mazzini	VDRL Slide	Kolmer
1	0	2	0	000000	±	1	0	300000
2	4	2	3	444400	4	3	3	443000
3	3	1	2	000000	3	2	3	000000
4	±	4	3	443000	4	4	1	430000
5	0	±	2	431000	0	±	0	100000
6	0	1	1	100000	0	1	1	100000
7	4	2	±	000000	4	2	±	000000
8	3	1	1	443000	3	1	1	100000
9	4	3	±	444440	4	3	1	444440
10	0	0	1	432100	0	0	1	100000
11	0	0	2	000000	0	0	2	000000
12	2	4	4	444200	1	4	4	443100
13	0	0	4	000000	0	0	4	AC
14	±	±	0	000000	±	4	0	430000
15	2	2	±	000000	4	4	±	443100
16	0	±	2	000000	0	0	2	000000
17	0	1	±	000000	0	2	±	000000
18	0	1	4	000000	0	2	4	431000
19	2	3	2	000000	4	3	2	210000
20	4	3	4	AC	4	3	4	AC
21	4	4	4	444200	3	4	4	444200

The results of comparison of serum with isotonic oxalate plasma in 21 treated cases are shown in Table IV In general, it appears that agreement is quite good, certainly with frank positives as it was with twenty additional negative cases In the treated cases the serum flocculation tests agree with the plasma tests, revealing a slight tendency towards greater sensitivity In the treated cases with the complement-fixation test there is less agreement Quite frequently the plasma appears more sensitive, but it also is occasionally less sensitive In one case the plasma was anticomplementary whereas the serum was not These equivocal results are rather difficult to interpret without larger sampling, and more studies will be required on larger series of cases to ascertain if this represents a true increase in anticomplementary results

Discussion

When blood samples that are later to be employed in sero-diagnostic tests for syphilis are treated with anti-coagulants, it is as well to remember that altering ionic content of a serum also changes the reaction in various flocculation tests (Burdon and Bromberg, 1930, Burdon, 1932) Substitution of bivalent ions produces positive tests, while substitution of univalent ions produces negative tests (Breazeale, Reusser, and Pierce, 1946) Kimball and Kabler (1948) have shown that chloride ions may interfere in complement-fixation tests, or may affect the flocculation tests (Green and Shaughnessy, 1942, Kline, 1942) On the other hand it has been shown that sodium oxalate in amounts up to 0 001 g per ml blood has no effect on complement-fixation tests (Watanabe, 1919) Potassium oxalate in optimal concentrations has been shown to give, with the plasma so obtained, results comparable to serum in sero diagnostic tests for syphilis (Coleman and Appleman, 1954), and calcium ion appears to protect complement from spontaneous inactivation (Lepow, Pillemer, and Ratnoff, 1953) Ecker, Castro, and Seifter (1945) report that strong electrolytes, such as chloride, bromide, and iodine with sodium, potassium, or ammonium in final dilution above 2 per cent, will increase the sensitivity of a serum, and that the concentration of electrolytes can be raised to a degree that will decrease the normal inhibiting factor present in fresh serum which is usually destroyed by heating at 56° C for 30 min In the results reported here the potassium level never reached a concentration sufficient to have a measurable effect in the tests used, but where both ammonium and potassium ions were present, the precipitation tests did appear to be somewhat more sensitive Using thymol-sodium fluoride the flocculation tests were more sensitive, but this apparently causes a loss of specificity This conclusion should be tempered by the fact that only a few sera were tested There is in this plasma, as well as in the sodium citrate plasma, a greater increase in the final concentration of sodium ion

The results indicate that heparin plasma also tends to be more sensitive in the flocculation tests, and that heparin destroys complement to a minor degree This concurs with the work of Wising (1937), who reports that calcium and sodium heparins destroy complement even in dilutions of 10^{-6} In the Kolmer test, using proper controls, this is usually no problem, as there is sufficient excess of complement More serious objections to heparin are that good samples are not always available and that it is not readily soluble as a powder The relatively colourless nature of the material when in a dry film on the walls of a blood-taking tube can also be disadvantageous

It has been noted that the natural heparin concentration in the blood may be quite different in various individuals (Ziff and Chargaff, 1940) It has been demonstrated recently (Freeman, Engelberg, and Dudley, 1954) that perhaps heparin is normally present in the blood in amounts considerably greater than was previously thought The potency of heparin is not precisely correlated to the sulphur content, yet the removal of the sulphur radicle inactivates its action as an anti-coagulant (Wolfrom and McNeely, 1945) Sulphur may play a part in the haemolytic activity of complement Yamakawa (1943) reports that complement depends upon a redox system containing sulphydryl groups A further effect of heparin as an anti-coagulant is that the blood calcium is left in solution in a heparinized preparation (Holt, 1931), whereas with many of the other anti-coagulants the calcium is precipitated or bound in a weakly dissociated compound This excess calcium is then available in levels approaching that of normal serum to add its stabilizing effect to the calcium In an electrophoretic study of the effect of heparin on human plasma proteins (Chargaff, Ziff, and Moore, 1941), it was noted that a globulin fraction moving with the mobility of gamma globulin was not attacked by heparin It was conjectured that the acidic groups of the anti-coagulant molecule serve to arrange the albumin molecules around it Perhaps this sparing action of the gamma globulin is the reason sero-diagnostic tests and other antibody estimations can be done frequently on heparin plasma

From the evidence presented it would appear that the anti-coagulants certainly do not interfere with the release of antibody It would seem that nothing in the "step-wise" completion of the clotting mechanism is needed for the appearance in plasma of reagin of syphilis at levels equivalent to serum as measured by the tests used

The results would indicate that many anti-coagulants apparently make sero-diagnostic tests more sensitive Further studies of larger numbers of blood samples are needed to determine if this represents an increase in sensitivity without a loss of specificity

Summary

(1) The level of reagin antibodies of syphilis as measured by the standard Kahn, Mazzini, VDRL slide, and Kolmer tests in blood treated with heparin, sodium citrate, thymol-fluoride

mixture, and potassium-ammonium oxalate mixture, has been shown to be equivalent to that in serum

(2) The addition of these anti-coagulants appears to make the flocculation tests slightly more sensitive

(3) The completion of the clotting mechanism is not required for the release of these antibodies

(4) Some of the anti-coagulants destroy complement to a small but capricious degree

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Brit J vener Dis (1955), **31**, 113

PROSTITUTION*†

BY

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There are two main approaches to the problem of prostitution the medical and the social To the venereologist the chief interest in prostitution must be that it provides the main reservoir of infections and re-infections But in comparison with the social approach, the medical aspect presents a simple problem

In 1949 the British Social Biology Council undertook a small survey‡ of prostitution in London The first step, mainly statistical, was undertaken jointly with the London School of Economics and consisted of an examination of the records of Scotland Yard, which was carried out by permission of the Commissioner of Police, Sir Harold Scott As it was not possible to study all existing records of prostitutes it was decided to take those of one year immediately after the second world war and one year in more normal times The years 1946 and 1949 were accordingly chosen We extracted from the records the comparative statistics for soliciting and other relevant offences, the ages of prostitutes involved, the number of their arrests and other charges against them, as well as the numbers of prostitutes convicted in both years, and so on A detailed analysis of a random selection of 150 case records was then compiled, and from these we have obtained information about the place of birth of the prostitute, her total number of charges for soliciting, changes in districts, and age of first conviction, the number of years between her first and most recent conviction for soliciting, her nationality, her juvenile and adult police record, with the type of offence before and after conviction for soliciting We also obtained information where possible, on the education she had received, her home conditions, her previous occupation her age on coming to London, her marriage, the number of children, her consorts, her criminal associates, and her personal and social situation on becoming a prostitute

Talking about prostitution has certain very real handicaps the first is that there is so little written material on which to draw Outstanding publications include those of Flexner (1914), Freed (1941), Glover (1945), Hewitt (1951), and Bennett (1954) Surveys have also been undertaken by the League of Nations (1938a, b, 1943) and the Los Angeles Dept of Public Health (1945) There is very little else that is new, beyond the startling statement from Russia that prostitution has been abolished there

A second difficulty is that, while factual knowledge that can be checked is meagre, the veritable jungle of folklore surrounding the subject tends to cloud one's thinking

It is also a subject which brings the emotions into play, for I need only remind you that prostitution, regarded as the exploitation of women by the male, has been, and to a lesser degree still is, linked with the struggle for female emancipation and equality of the sexes

Types —It is impossible and unwise to attempt to describe " a prostitute type ' They vary enormously in age, in intelligence, in social class, they may be married or single, they may come from country or town, they may be physically sound or grossly handicapped But it is significant that the prostitutes who have been studied by research workers have almost inevitably been the failures, those who have been through the courts, or have broken down and needed social and medical treatment Our knowledge of the successful prostitute, who does not need help and has no police record, is practically non-existent

It does appear from the available material, however that they do come mostly from a poorer economic background But even this conclusion

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† Read to the M S S V D November 27 1954
This survey was published by the British Biology Council (1955)

should be treated with caution, for it may also indicate that the early school-leaving age has something to do with it too, not to mention poor housing In Johannesburg, on the other hand, where conditions are very different, it is clearly shown that poor wages for women workers are the main cause of prostitution

The suggestion frequently made that prostitutes are mainly of poor intelligence should also be received with caution We have not the necessary data on the successful prostitute on which to base a judgment

We need to know much more about the precipitating causes, the family background and so on, before we can even make a guess at why one girl becomes a prostitute and another girl in similar circumstances does not There is an enormous amount of work still to be done in this field and, until a full-scale research is carried out, any opinions can only be personal ones It is much to be regretted that grant-giving bodies appear to have placed a taboo on the subject

But once having crossed the line to prostitution, the girl becomes a member of a minority group, not actively persecuted but definitely ostracized, and she swiftly develops the psychological attitudes of such a group She is at war with society, and loses what sense of responsibility for her actions she may have had To the outsider—and this includes the client—she lies only too easily and pleasantly about herself She has a tremendous loyalty to other prostitutes, though this loyalty may not last very long, for violent quarrels and reconciliations are part of her everyday life She will rush to help any friend in difficulty and smother her with kindness regardless of the cost It has been suggested that this extreme generosity is a compensatory mechanism and is really a form of "mothering" For prostitution in itself is a rejection of maternity and the prostitute s guilt feelings, recognized by her or not, as well as the claims and fulfilment of her biological function, find an outlet in this maternal attitude to a sister in trouble, and here probably lies the explanation of the attitude of the better type to her male customer Often, however, this extreme generosity, though genuine, may be quite superficial The friend she is helping is perhaps in hospital or prison, yet she will not hesitate to go to her room in her absence and steal her belongings One reads too reports in the papers of how she will defend her "beat" from intruders, using physical violence on occasion The prostitute is not as a rule the oversexed girl who enjoys the physical side of her life Indeed, she takes a pride in the fact that she is frigid with her client whom she despises quite as much as he despises her She nearly always has a man friend in the background, however, with whom she finds her satisfaction, and by whom she may even have a child or children He very often acts as her "ponce" and plays a very important part in her life, giving her some sense of security, and easing her essential loneliness

I would stress again that most of our knowledge about prostitutes comes from the study of the unsuccessful ones, those who have police records, or those who have fallen on evil days We know little of the successful ones There is a certain type, however, whom one cannot ignore the refined and kindly prostitute who acts as a friend to the lonely man and appears from his accounts to be thoroughly decent One is told so often about her that she must exist in some numbers, but the only one of this type whose history, as told to the client, I have known to be checked, turned out to be a very different person from the picture given by the client Instead of being a heartbroken war-widow with a child to educate, with nothing left in life except the desire to help others (the others, of course, being men in search of sexual companionship), she turned out to be single, but living with a criminal, and with a record herself of receiving stolen goods Perhaps it is cynical, but I should like to suggest the possibility that some of these "good sorts" may be the top-level experts at their job who cash in on the needs of the lonely man whose marriage and sex life are unsatisfactory For it is the prostitute's job to give the man the satisfaction he asks for and in the way he wants it, and it is the measure of her skill that she appears to do it with such success And, in parenthesis, I should like to add that if more women understood and studied the art of being wives instead of taking their position for granted, there would be a sharp decline in the number of prostitutes and many more happy and lasting marriages Yes, some wives could learn a great deal from some prostitutes !

Link between Prostitution and Crime —The link is a real one, but the prostitute herself is, as a rule, guilty of only minor offences For a woman prostitution is accepted as the crime *par excellence*, and one should bear this in mind when studying criminal statistics But while she herself may not have a bad criminal record, she does associate with criminals Out of 150 prostitutes in our survey, 64 were known to have associated at some time with men and women (not prostitutes) who were criminals 72 men who associated with these 64 prostitutes had crime records ranging from larceny (27), house breaking (sixteen), and assault (ten), to shooting a police constable on duty (one)

Not only is the link with crime a real one, but there is an even darker side to the picture, for where prostitution exists among the wealthier sections of a community, it is inevitably tied up with vice and perversions, and this must not be forgotten if we are to form a true picture of what prostitution involves Prostitution is not legally a crime, any more than adultery or fornication, but it acts as a kind of magnet that attracts to itself the worst elements of society, the third party exploiter, and the criminal For this reason alone we cannot be indifferent to the problems it presents

The Call-Girl System —This is a comparatively new development in prostitution, and seems to have superseded the brothel to a large extent, though once again the factual evidence for this is lacking The system has developed with the introduction of the telephone, and in the U S A , where it is the policy to clear prostitution off the streets, is more highly organized than in this country Here is an example of one way in which the system works there is a *tobacconist in the West End* where a man can go and say he wants a woman , he is then shown several albums of photographs from which to choose the girl he fancies , this done, the tobacconist pushes over a card to the customer and gives him a telephone number to write down The tobacconist charges a guinea for this service, and the girl charges three guineas for about half an hour, or five guineas if she is taken out to dinner first The flat where she *is visited is usually in a very respectable block*

An interesting point about this system is that here the amateur and professional girls meet, for the good-time girl the young and silly girl out for adventure, perhaps even the student trying to get through her course on an inadequate allowance, and the professional prostitute are all found among the call girls Its disadvantage as against street importuning is the opportunity it gives for exploitation

Remedies —In considering possible answers to the problems presented to us by prostitution, one must be realistic Unless one can offer the prostitute very high wages for irregular hours of intermittent work which is interesting and exciting involving contact with members of the opposite sex, she is not likely to alter her way of life Temperamentally, and if she has been at the game for long, she is unfitted for the daily round of routine work After all, she has become a prostitute because she is a misfit and is maladjusted to society, and she remains one because she has found a circle in which she is accepted and a way of life that offers her the things she wants—easy money, no responsibility, and no necessity for regular hours of work, even though it does involve hardship and even danger I do not suggest by this that we should not keep the way open for her if she wishes to rehabilitate herself, for we most certainly should, and our survey has shown that she is aware of the possibilities and means of doing so But I do not think that we are going to make much headway by a direct approach to the well-established prostitute

Something, however, could and should be done to make the conditions of the trade such that it will not be attractive to the young recruit It is our duty and responsibility to the younger generation *to do so, and by far the greatest responsibility* that we have to the prostitute and potential prostitute Short of penalization, we should take every possible step to achieve it It is interesting that quite a number of established prostitutes, when asked about their profession, have expressed grave concern for the younger ones under 21 years, and have even urged that they should be taken right away off the streets, by force if necessary, in an attempt to induce them to give up the game before it is too late The process of " putting back " a young prostitute for a medical examination now used by some magistrates is a step in the right direction, and could, I think, be developed much further It is, in my opinion, the strongest argument in favour of increasing the fine, that it will deter at least the beginner and the older prostitute, and may be the cause of their quitting the profession Let us get the idea out of our minds that the prostitute's position today is the same as it was in 1870, when she was a victim of poverty and preyed upon by society She is indeed still to be pitied but for different reasons, for now it is she who, driven by no economic compulsion, preys upon the community Why then should we not make the conditions of her profession as difficult for her as possible ?

Having said this, I would make a qualification here about economic necessity Up to quite recently it has been the policy of voluntary agencies to use every possible persuasion to insist that the unmarried mother should keep her baby, regardless of her circumstances and family background But at the same time, unbelievably, no record has been kept or follow-up done into the results of this policy We know that many prostitutes have illegitimate children (22 per cent in the survey) I would suggest that this policy may well have helped to swell their ranks, for it is a very difficult economic problem to provide for two people out of a small pay packet, especially when one of them is a young child The fate of the prostitute s child as it grows up hardly bears thinking about

The indirect approach to the problem is surely the most hopeful Supply should in every way possible be prevented from creating the demand, even though the economist may shudder at the thought It has been said that 15 per cent of men will find a prostitute however difficult it be, another 15 per cent will not go near one however readily available, and the remaining 70 per cent will go to one if it is made more or less easy It is this 70 per cent that should interest us, and to whom we owe it to keep the streets as clean as we can

There is another point which cannot be ignored Have we not also a responsibility to the young man who has left school and is starting out in life? Do we not owe him something too? Should we not try to give him some protection from the prostitute, who is always ready for him when he is particularly vulnerable after an evening's amusement?

We know that certain social and home conditions are conducive to anti-social behaviour, one can only just touch on them Freed (1941) indicated that there may be a correlation between prostitution, the marriage rate, and the number of unmarried women in the population If he is correct, then we should aim at removing all obstacles to early marriage Bad housing too plays its part and is a contributory factor to prostitution, for overcrowding, with the whole family sleeping together in one room, cannot afford a good start in life and one cannot blame the girl who will do almost anything to escape from such conditions As it is, she acquires a precocious knowledge of sex in the worst possible way, which makes it all the easier for her to take to the game

This brings me to the vexed question of sex education Much has been done and many hopes have been raised by its widespread adoption Indeed, prostitutes have often given their ignorance about sex as one of the factors in their taking to the life This ignorance will be confirmed by anyone who has worked in a fertility clinic, where quite a number of couples who come for advice have never consummated their marriage through sheer lack of knowledge But one may have a comprehensive knowledge of the anatomy and physiology of sex, and yet that knowledge may be of no help but rather may be a positive hindrance if one's attitude towards sex is wrong And this leads one to the heart of the problem of prostitution—it is this too generally accepted divorce of sex from its true context expressed in the love of a man and a woman Love and sex are a unity, when they cease to be so and become a dichotomy, you have their incomplete and immature expression in isolation, on the one hand in prostitution, and on the other in a romantic celluloid love based solely on emotion without knowledge

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EIGHTEENTH-CENTURY V.D. PUBLICITY *

BY

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London

It was fortunate for E Johnson, proprietor of the *British Gazette and Sunday Monitor*, that, in the late eighteenth century, it was not a penal offence, as it has been since November, 1917, to advertise to the lay public remedies for the treatment of venereal disease In the files of this newspaper for the years 1789, 1790, 1791, and 1792, there appeared, week after week, among the advertisements for boarding-schools, dancing-lessons, toothache-cures, and so on, the names of "cures" for V D It is odd to think that just over a hundred years later, in 1909, Brieux's play *Les Avaries* should have been banned because the subject of venereal disease was taboo !

The advertisement for Dr Arnold's Pills, which were to be bought for 10*s* 6*d* and one guinea a bottle at the doctor's house, 7, Gough Square, Fleet Street, read thus

> Though mild and innocent in their nature they have been found by long experience to be an invaluable remedy for the V D and have effected a cure where salivation would fail
>
> The pills were prepared
>
> for those who have injured themselves by intemperance, and young people who feel in the prime of life the dreadful effects of a secret vice too frequent among the youth of both sexes

Another advertisement informed the reader that Mr Spilsbury, junior, had appointed Mr Jolly, chemist, King Street, Carnaby Market, "to vend for him his valuable medicines", which included his "alterative drops for Venereal complaints" These could also be obtained at Spilsbury's dispensary in Soho

At Randalls, the Royal Exchange, was to be bought, at 5*s* 5*d* and 10*s* 6*d* a bottle, "Specifique Unique", a V D cure which was offered "by a professional man whose new discovery offers a certain cure for gonorrhea within one week" To prove that "to benefit mankind" was his main motive, "any pauper recommended by a respectable inhabitant will have the cure gratis"

"Gleets" could be cured, the advertiser claimed, by "Balsam of Life", at 6*s* 3*d* a box, for those whose constitutions were debilitated by "dissipated pleasures, the immoderate use of tea, etc" As an antidote to mercury, which was used in the treatment of venereal disease, there was "Hunter's Restorative Balm" which was advertised as "a restorative medicine for life and health, for recovering lost vigour, recruiting impaired strength, and giving new life and vigour to debilitated old age and emaciated youth" Another antidote to "the dreadful consequences of mercurials" was Mr Beer's "Grand Arcanum" Dr Blagrave's "Golden Spirits" were advertised for the cure of eruptions" due to intemperate living"

One of the most widely advertised cures was Leake's "Pilula Salutaria", more commonly known as "Leake's Pills" These were prepared and sold by Thomas Taylor, a member of the Corporation of Surgeons, at 9, New Bridge Street They cost 2*s* 9*d* a box, and were, according to the advertisements

> justly famous for curing, in all its stages, the Venereal Disease One small pill is a dose One box in a recent case brings speedy recovery It will effect a cure when salivation and other methods all avail nothing

Forty thousand of both sexes were reputed to have been cured in 8 years

The advertisement for Leake's Pills in the issue of the *British Gazette and Sunday Monitor* for March 19, 1792, contained a letter to Thomas Taylor from Richard Edwards, clerk of St Michael's Church, Bristol, witnessed by John Morris This told of a mariner living in Church Lane in that parish, who was a free burgess, and had contracted V D at Bordeaux The first effects were soon removed by medicine But, soon, alarming symptoms appeared He had excruciating pains in his head He lost his hair, his sight, and his hearing He had such pains in his legs that he could not walk, sit, or lie, without being in agony There were swellings inside each thigh He seemed to be dying when Richard Edwards went to visit him, but Edwards remembered reading, in the *Bristol Mercury*, of the cure of one, James Joshua Jones, by Leake's Patent Pills

The dying man agreed to try the pills, and within a fortnight, he could hear, see, and walk, the swellings on his thighs soon disappeared, and before long, he was expected to be back at sea He had begged Edwards to write to surgeon Taylor to "offer thanks for such an amazing restoration to health from the brink of the grave"

* Received for publication December 3 1954

The Leake whose name was associated with these pills was not John Leake, the man midwife who died in 1792, but Walter Leake, a journeyman bookbinder, who took out a patent for the pills taking advantage of the fact that he bore the same surname as the doctor In 1767, Dr John Leake had published a "Dissertation on the Properties and Efficacy of the Lisbon Diet Drink and its Extract in the cure of Venereal Disease", a discreditable production in which the composition of the remedy is kept a secret while its efficacy in more than thirty diseases is maintained *

This "Dissertation" was still being advertised, more than 20 years later, in the *British Gazette and Sunday Monitor*, as a handbook telling how to cure V D, but sales of the book had been badly affected by the sale of Walter Leake's pills which were said to obtain the same results as the Lisbon Diet Drink In the meantime Dr John Leake had bought a piece of land near the Surrey end of Westminster Bridge, and persuaded subscribers to build a Lying-In Hospital there, and appoint him first physician

Another book advertised in this newspaper was "Salivation Exploded or a Practical Essay on Venereal Disease fully demonstrating the inefficacy of Salivation and recommending an approved Succedaneum which gives a different method of preventing Infection" (2*s*)

Books, pills, and balsams, would benefit only the literate, or well-to-do

For the poor there was the Lock Hospital, Grosvenor Place, but only comparatively few could be treated there In "London and its Environs" (1761), it is stated that between the opening on January 31, 1747, to March 10, 1753, 1,740 in-patients had been discharged as cured, and there were also a few out-patients Admission to the Lock Hospital was not easily gained, according to the rules, no patient could be accepted without a recommendation in writing signed by a Governor, or one of the weekly committee To be a Governor, a gentleman had to give a minimum annual subscription of £5 Every Saturday, a committee of at least five met at the hospital at 10 a m to admit and discharge patients, adjust the weekly accounts, receive the reports of the visitors, and examine the affairs of the house Two of the contributors were appointed weekly by the committee to conduct a daily examination of the behaviour of the patients and nurses All recommendations for admission had to be received on a Saturday morning Every patient had to submit to the rules of the hospital, on pain of being discharged for irregularity, after which he could never again be received "on any recommendation whatsoever" No Governor could have more than one patient in the hospital at any one time, and preference was given to patients recommended by "those who subscribe the largest sums", but an exception was made in the case of "several married women, children, and infants", who were often "almost naked, pennyless and starving" In the first 6 years over sixty children between the ages of 2 and 12 were treated as priority cases because

> They became infected from ways little suspected by the generality of mankind, from the absurd opinion, imbibed by the lower class, both males and females, that by communicating this loathsome disease to one they found, they will get rid of it themselves, and from this principle, which is contradicted by human experience, the most horrible acts of barbarity have frequently been committed on poor little infants, and thus these vile wretches have entailed the most dreadful disease on these innocent infants without affording the least relief to themselves This the Governors have thought their duty to publish in order, as much as possible, to root out among mankind an opinion at once so base, so false, and productive of such cruelty

As late as 1908, when Shaw wrote his preface to "Getting Married', he mentioned that forcing contagion on another person by act of violence was "still punished unmercifully by an extreme term of penal servitude when it occurs, as it sometimes does, through the hideous countryside superstition that it effects a cure when the victim is a virgin"

In 1761 there was also a Lock Hospital for venereal disease in Kent Street, Southwark, it was a former leper hospital, belonging to St Bartholomew's There could not have been room for many patients there, because it is described as "a small neat edifice" Another hospital, The Lock, in Kingsland, at that time "a hamlet of the parish of Islington", had also been a leper hospital before St Bartholomew's and St Thomas's appropriated it to the cure of venereal disease In this instance the "edifice" was a plain modern brick building without ornamental decorations It is large, and proper for the use to which it is applied, and on the end of it is a dial which has the following suitable motto "POST VOLUPTATEM MISERICORDIA" Though no letter from a governor was required for St Bartholomew's patients, there was a real deterrent to the admission of the poor, for they had to deposit, or give security for, the payment of a guinea in case of death, for the funeral Thus, "some of the poorest and most miserable and consequently the most proper objects" were "unhappily excluded from reaping the benefit they might otherwise receive"

*DNB

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LOCAL TREATMENT OF TRICHOMONAS VAGINITIS*

BY

R D CATTERALL and MARY WILLIAMSON

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There is general agreement that the treatment of trichomonas vaginitis is unsatisfactory Medicaments administered by mouth or parenterally have proved ineffective, and although the immediate response to some remedies applied locally is satisfactory, there is a marked tendency to relapse There seems little doubt that the preparations which seem effective do no more than temporarily suppress the signs of infection in many cases It is sometimes necessary to maintain suppressive treatment for many months before cure can be presumed and in some cases there are frequent relapses despite prolonged treatment of all kinds

The value of local remedies must be assessed by the degree and speed with which the clinical effects of vaginal discharge, intertrigo, dyspareunia, and pelvic pain are abolished, and, in the course of observation and tests, by the proportion of cases in which the patients remain free from relapse Assessment requires a considerable period of observation, and testing is complicated by the fact that many patients discontinue attendance when their symptoms are relieved, and that with outpatients there is no means of distinguishing between re-infection and relapse

The necessity for prolonged treatment in many cases renders it imperative that remedies should be well tolerated and that patients should not readily become sensitized to them

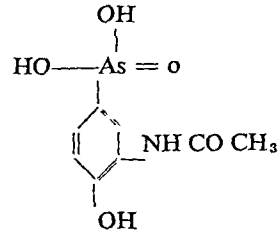
The standard preparation which has been used for a number of years is acetarsol It has proved the most effective of the many remedies which have been tried and recommended, and in general it is well tolerated It is, however, an arsenical preparation and cases of sensitization have been reported Most of these, which occurred after prolonged treatment with acetarsol vaginal pessaries or powder used intravaginally, were manifested by a generalized exfoliative dermatitis, pyrexia, and malaise (Kesten, 1938, Doyle, 1952) Some patients had been previously sensitized by arsenical compounds for the treatment of syphilis and showed immediate symptoms of sensitization on beginning a subsequent course of acetarsol vaginal pessaries (Campbell, 1937, Orchard, 1951) Thus there is always the possibility that arsenical exfoliative dermatitis may develop, and patients who have been sensitized to the organic arsenicals in the past run an extremely grave risk if acetarsol is used It is therefore desirable that an equally effective alternative drug belonging to some other chemical group should be available, such a drug may also prove effective in cases which prove resistant to acetarsol

* Received for publication August 25 1954

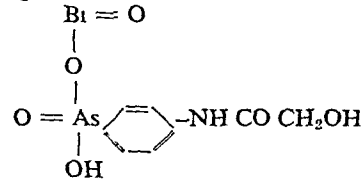
Present Investigation

The following compounds have been used —

(1) **Acetarsol** —This is a pentavalent arsenical compound, 3-acetamido-4-hydroxyphenylarsenic acid, containing 27 per cent arsenic, with the following structural formula

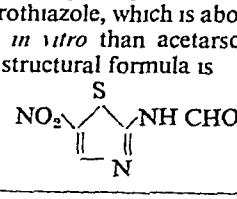


(2) "**Milibis**" (as marketed) —This compound is bismuthoxy-4-N-glycolylarsanilate, it contains approximately 15 per cent arsenic and 42 per cent bismuth, the structural formula being



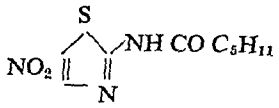
(3) Milibis contained in a more soluble base

(4) "**Aroxine**",* a pessary containing 100 mg 2-formamido-5-nitrothiazole, which is about one hundred times more active *in vitro* than acetarsol (Bushby and Copp, 1955) The structural formula is

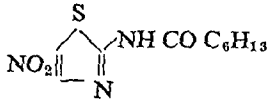


* 'Aroxine' is the trade name for the pessaries (Burroughs Wellcome Ltd)

(5) Pessaries containing 100 mg 2-hexanamido-5-nitrothiazole, 40 C 53, an analogue of 2-formamido-5-nitrothiazole, with the structural formula



(6) Pessaries containing 100 mg of the higher homologue of 40 C 53, 2-heptanamido-5-nitrothiazole (41 C 53), with the structural formula



During 1953, 215 patients with trichomonas vaginitis were divided into six groups, each of which was treated with one of the preparations enumerated The immediate results of treatment were recorded and an attempt was made to follow these patients with frequent examinations and tests for at least 3 months Many had first infections but some had relapsed after earlier treatment In all but the last group, the method of treatment employed was to insert two tablets of the compound to be tested high into the vagina each day for periods varying from 7 to 14 days On the first occasion the tablets were inserted by a member of the nursing staff and the patient was instructed in the technique of self-treatment Thereafter the patients continued their own treatment without immediate supervision

It was necessary to establish arbitrary criteria of cure, as follows

(*a*) There must be no clinical evidence of vaginitis for at least 3 months after completion of course

(*b*) Smears from the vaginal secretion must be negative for *Trichomonas vaginalis* during the same time, which must extend over three menstrual periods

At the end of this time patients were discharged provided that they were free from associated infections such as gonorrhoea or syphilis

The patients treated included married women and single women, of whom some were prostitutes and others of promiscuous sexual habits If no condition other than trichomonas vaginitis was found they were informed that they were not suffering from a venereal disease but were urged to regard the condition seriously This policy of reassurance, which was ethically correct, affected the investigation adversely, for many took a light-hearted view of their disease and either did not follow instructions conscientiously or failed to continue attendance Some patients were of low intelligence, so that occasionally tablets were not properly inserted and were found lying between the labia Two patients inserted the tablets into the rectum and four even took the tablets by mouth No distinction was possible between patients who relapsed and those who were re-infected, and therefore all who showed evidence of infection after treatment were included among those who were considered to have relapsed All those who ceased to attend received two letters renewing their appointments but the response to correspondence was uniformly poor throughout the series All these factors added to the difficulties of assessment

Results

1 Acetarsol and Aroxine—Of fourteen patients, all of whom had experienced relapse after various remedies, four received acetarsol and ten Aroxine The method of treatment was to insert two tablets vaginally each night for 7 nights

All four patients who received acetarsol and five who received Aroxine defaulted The remaining five patients made an immediate satisfactory clinical response and microscopic tests for *T vaginalis* became negative Two relapsed, however, after 1 month and three after 2 months These results suggested that Aroxine was an effective remedy but probably required to be used for more than 1 week

(2) Aroxine—All of 39 patients who had been treated with acetarsol and had subsequently relapsed were treated with Aroxine by vaginal insertion of two tablets each night for 14 successive nights

Sixteen patients defaulted and seven relapsed within 1 week of the cessation of treatment Four patients relapsed after 1 month, five after 2 months, and three after 3 months Three patients were cured In one case treatment was discontinued because of vulval irritation (see Table I)

TABLE I
RESULTS IN SERIES 2

Results	Aroxine
Defaulted	16
Cured	3
Relapsed after 1 week	7
Relapsed after 1 month	4
Relapsed after 2 months	5
Relapsed after 3 months	3
Treatment discontinued	1
Total Patients	39

One of the five patients who relapsed after 2 months developed acute bilateral salpingitis but the gonococcus was not found in the secretions Two patients who relapsed were subsequently cured by further administration of acetarsol

In view of the evidence that the immediate effect of Aroxine seemed to be as satisfactory as that of

acetarsol, it was decided to institute a comparison between these drugs in a larger number of cases

(3) **Aroxine and Acetarsol Compared**—The investigation was limited to patients in whose secretions trichomonads were discovered for the first time All had recently come under observation and were, as far as could be judged, cases of fresh infection Alternate patients were treated with Aroxine and acetarsol by the intravaginal insertion of two tablets each night for 14 successive nights Of the 99 patients treated, 23 of those receiving Aroxine and 26 receiving acetarsol defaulted Five cures were obtained with Aroxine and six with acetarsol Five patients relapsed within 1 week of the course of Aroxine while only one relapsed in a similar period after acetarsol Of patients who relapsed after 1 month, seven had received Aroxine and six acetarsol, at 2 months eight relapsed after Aroxine and eight after acetarsol, at 3 months, one relapsed after Aroxine and two after acetarsol One of the patients who received acetarsol had the treatment discontinued because of local soreness and irritation (Table II)

TABLE II

RESULTS IN SERIES 3

Results	Drug		
	Aroxine	Acetarsol	Total
Defaulted	23	26	49
Cured	5	6	11
Relapsed after 1 week	5	1	6
Relapsed after 1 month	7	6	13
Relapsed after 2 months	8	8	16
Relapsed after 3 months	1	2	3
Treatment discontinued	—	1	1
Total Patients	49	50	99

Three of the patients who relapsed after treatment with Aroxine were subsequently cured by the administration of acetarsol

Because of the large proportion of defaulters it was not possible to draw conclusions from this comparison, but as far as the evidence went there appeared to be no great difference between the effects of the two drugs, although the higher proportion of immediate relapses after Aroxine is perhaps worthy of note

(4) **Pessaries containing Analogues of 2-formamido-5-nitrothiazole**—These were used for trial in cases which had previously relapsed These substances are less soluble than 2-formamido-5-nitrothiazole and were tried in the hope that the antitrichomonal activity would be more prolonged

(*i*) Fourteen patients were given Aroxine seven relapsed within 2 months, three defaulted, and four were cured

(*ii*) Eleven patients were given 40 C 53 four relapsed within 2 months, six defaulted, and one was cured

(*iii*) Eleven patients were treated with 41 C 53 six relapsed within 2 months, four defaulted, and one was cured

The results were inconclusive but it seems that these analogues had no particular advantages over the original (Table III)

TABLE III

RESULTS IN SERIES 4

Results	Drug		
	Aroxine	40 C 53	41 C 53
Defaulted	3	6	4
Cured	4	1	1
Relapsed after 1 or 2 months	7	4	6
Total Patients	14	11	11

(5) **Milibis**—Twelve patients were treated by the vaginal insertion of two tablets of Milibis nightly on ten consecutive occasions The results showed that no patient was cured, three relapsed after the first month, seven showed trichomonads in the secretions during the course of treatment with no evidence of clinical improvement and two defaulted (Table IV)

All these patients complained of dryness, soreness, and vulval and vaginal irritation They also complained of difficulty in inserting the tablets which were so insoluble that on examining patients the vagina was found to contain undissolved tablets In view of the lack of an immediate satisfactory effect and the local reactions which the majority of patients experienced, it seemed clear that this preparation was unsatisfactory

The makers then supplied a preparation contained in a more soluble base, and this was used in the treatment of ten patients who received a similar course lasting 10 days Results showed again that no patient was cured, three relapsed in 1 month and two showed relapse within a week Five patients defaulted (Table IV)

TABLE IV

RESULTS IN SERIES 5

Results	Drug	
	Milibis	Modified Milibis
Defaulted	2	5
Cured	0	0
Relapsed during treatment	7	—
Relapsed after 1 month	3	3
Relapsed in 1 week	—	2
Total Patients	12	10

The modified preparation did appear to dissolve in the vagina more satisfactorily, but dried residue was found on routine examination in most patients Only three patients showed evidence of clinical

improvement and all three relapsed and showed positive smears at the end of the first month These three patients were subsequently cured with acetarsol There seemed no indication to pursue investigation of this preparation

(6) Irrigation and Local Application—The unsatisfactory results which followed these forms of local treatment might be due to the fact that the trichomonicidal agent which was applied in the form of small vaginal tablets did not reach all the folds and rugae of a canal which, on distension, is fairly voluminous Another possible source of error was that reliance had to be placed upon the patient for proper insertion of the tablets The effect was therefore tried of using a single treatment in which the vagina was thoroughly irrigated with 0 2 per cent solution of 2-formamido-5-nitrothiazole followed by the application to the vaginal walls of paste containing 1 per cent of the drug

Technique

The patient was placed in a modified Trendelenberg position and the vaginal wall was stretched by means of a Cusco's bivalve speculum of appropriate size The solution was injected into the vagina with a Ritchie's bladder syringe After three successive irrigations by which the walls and fornices of the vagina were exposed to the solution, the cavity was filled with the fluid which was left in position for 20 minutes Previously it had been ascertained that the application of this solution in a similar concentration *in vitro* was lethal to the organism in 20 minutes The vagina was then emptied and the paste liberally applied to the vaginal wall The patient was subsequently allowed to go home

It was hoped that such thorough treatment given on one occasion would remove the responsibility of further treatment from the patient Five patients were so treated with satisfactory immediate response, but unfortunately all relapsed within one week Thus this form of local treatment also proved unsuccessful

Male Contacts—Ninety-seven males who were known to be contacts of the 215 women suffering from trichomonas vaginitis were examined In only four were trichomonads found in urethral smears or in specimens of urine after centrifuging, 62 of the male contacts, however, showed evidence of gonococcal urethritis and 32 of " non-specific " urethritis Five male contacts showed no evidence of urethritis although two of them had urethral strictures

Discussion

The methods used in these cases were unsatisfactory, like all other forms of treatment for trichomonas vaginitis Even the better preparations produced only symptomatic relief during treatment, with cure in a very small proportion of cases Subsequent relapse occurred in the majority of those who remained under observation

Within these limitations, acetarsol, in the course of long experience, has proved its comparative efficacy and has caused few toxic reactions The disease, however, is a chronic one and the likelihood of repeated relapse is considerable Therefore it is desirable that alternative drugs should be available if they can be shown to be reasonably effective Aroxine appears to be effective and non-toxic Only three patients out of 103 who were treated with this drug complained of toxic effects, two of these noticed local irritation and one experienced a more severe reaction which was apparently due to sensitization This patient complained of a burning sensation on the vulva on the fourth day of treatment and was found to have oedema of the labia Intradermal and patch tests with Aroxine proved negative and the condition subsided when the drug was discontinued and antihistamines were given by mouth Aroxine has the advantage that it is not an arsenical Acetarsol, which is an arsenical, has produced few sensitization effects, but the fear remains that, with long continued use, these effects may occur and prove severe and even fatal Those patients who have in the past become sensitized to the arsenical drugs run considerable risk if acetarsol is used for this very common infection without knowledge or appreciation of the significance of the earlier history From present experience it cannot be said that Aroxine is a better preparation than acetarsol or even as good in view of the high proportion of patients showing early relapse after its use, nevertheless it did give symptomatic relief to almost all the patients and must be regarded as a useful substitute

The number of cures obtained after using each drug was not insignificant and the proportion was increased by prolonging treatment and by changing from one drug to the other So little is known about the fundamental pathology of the disease that it would be difficult to draw conclusions from these facts It is possible that there is more than one strain of the parasite or that in certain circumstances the parasite is not susceptible to a single drug Some patients are resistant to all treatment and show immediate relapse after any drug A case in point was a patient who was kept in hospital for 3 months to exclude the possibility of re-infection, and was treated with acetarsol, Milibis, acetic acid, Aroxine and its analogues, and solution of Aroxine followed by the application of paste containing the drug In spite of continuous therapy negative

results to smears were never obtained for a longer period than 1 week There are no special features which enable such cases to be recognized before treatment and the cause of resistance remains obscure

Results with Milibis were unsatisfactory There was no relief from symptoms in the majority of patients and no regression of clinical signs The tablets failed to dissolve and caused discomfort and irritation The preparation was deficient in trichomonicidal power, for on more than one occasion vaginal smears showed active trichomonads among the crystals The modification of Milibis which dissolved more satisfactorily showed no greater efficacy

Summary

The treatment of trichomonas vaginitis is unsatisfactory No medicament is effective systemically, and although some forms of local treatment are immediately effective the condition is prone to relapse The assessment of any form of treatment is difficult because so many patients discontinue attendance and because there is no means of distinguishing between relapse and re-infection The standard remedy, acetarsol, is an arsenical and its use occasionally results in sensitization which may be dangerous It is desirable that an equally effective non-arsenical preparation should be available as an alternative

Clinical results obtained in the treatment of 215 cases of trichomonas vaginitis with acetarsol, Milibis, Aroxine, and some modifications are described

Milibis proved ineffective Aroxine (2-formamido-5-nitrothiazole) applied locally produced results which were comparable with, although possibly slightly inferior to, those obtained with acetarsol Analogues of 2-formamido-5-nitrothiazole had no particular advantages

The results of investigations in the cases of 97 male contacts of women suffering from trichomonas vaginitis are described

We should like to thank Mr Ambrose King, F R C S , for his advice and help and also Dr C S Nicol for his help and advice in arranging the series

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OBITUARY

ALEXANDER FLEMING, KT, MB LOND, FRCP, FRCS, FRS

Sir Alexander Fleming, who died suddenly on March 11, 1955, was buried in St Paul's Cathedral His discovery of penicillin made him one of the great healers of disease, but this achievement and the many honours showered upon him in the past decade failed to alter his innate modesty and simplicity Penicillin and the later antibiotics have produced profound changes in many branches of medicine and surgery That this is particularly true of venereology is readily apparent to those whose experience goes back before the penicillin era, and it is fitting that this Journal should add its own tribute from one of his colleagues at St Mary's Hospital to the many others which have already appeared

G L M McE writes

Those of us who knew Sir Alexander Fleming and even those who merely heard the paper he read before the Medical Society for the Study of Venereal Diseases in 1944, will endorse all that has been said in praise of that kind, quiet, modest man whom history already acclaims as one of mankind's greatest benefactors It is not generally known that Fleming took more than a passing interest in venereology and that he was one of the first in Great Britain to treat syphilis with Ehrlich's original salvarsan Later he was appointed pathologist to the London Lock Hospital and was one of the early contributors to the now encyclopaedic literature of the Wassermann reaction

Working under Almroth Wright, whose sole research tools consisted of a microscope, stains, glass tubing, and a plentiful supply of blood, mostly his own, it is not surprising that immunology became Fleming's main interest, and during the first world war, when working as a pathologist with the British Expeditionary Force, he demonstrated the uselessness of antiseptics in infected wounds, showing how they invariably killed leukocytes and thereby actually encouraged the growth of bacteria It was thus especially remarkable and even ironic that he of all men was responsible for the discovery of the most effective therapeutic antiseptic of all time

The impact of penicillin upon our own specialty has been nothing short of tremendous and can be properly appreciated only by those of us who practised in the years before the war when, even in well-regulated clinics, up to 50 per cent of the gonorrhoea patients became " chronic " and no less than 20 per cent showed complications of one kind or another Revolutionary though it was at the time, the success of the sulphonamides in gonorrhoea was comparatively short-lived, as resistant strains were with us from the start and after 7 years had to a large extent replaced the susceptible ones

In syphilis the well-tried arsenicals and bismuth, in addition to their toxicity, had the great disadvantage that their success depended largely on the cooperation and perseverance of the patient, whereas with penicillin even the ignorant and antisocial are made non-infectious and, as often as not, are permanently cured before their lesions have had time to heal This rapid sterilizing action undoubtedly explains the success of penicillin, not only in the control of venereal syphilis, but in the campaigns against the non-venereal treponematoses in various parts of the world

The writer will not forget the day in 1934 when Fleming first showed him the now famous contaminated culture with the terse, prophetic comment —" That stuff should be good for your patients ' — and how the subsequent discussion on ways and means ended with his saying—" It's up to the chemists now, I'm no chemist " Later, when the prophecy came true, he became seriously concerned lest low dosage should encourage strain resistance and, even in 1946, when syphilis was common and penicillin still expensive, he advocated a large and sustained dosage for all infections including gonorrhoea, ridiculing the danger of masking syphilis " Cure the two diseases ', he used to say ' How many will wait months for a final blood test ? " Of course we did not take his advice, but perhaps there was truth in what he said He was justly jealous of the reputation of his penicillin and was always delighted to hear that in syphilis and gonorrhoea the results remained as good as ever

BOOK REVIEWS

Physiology and Biochemistry of the Skin By Stephen Rothman 1954 Pp 741, 194 illus University of Chicago Press (£7 6*s* 6*d*)

This book was written to present a detailed study of the physiology and biochemistry of the skin, covering not only a major part of the past work on the subject but also presenting new and original theories and offering fresh lines of approach to problems as yet unsolved Throughout, the text is stimulating and full of interest and there is a particularly valuable and exhaustive bibliography If there is any criticism to make it is that the book is too comprehensive and that its detailed inclusion of past and sometimes outworn theories may be at the expense perhaps of more recent, although unproven work

The aim of the work has been admirably achieved and the result is a book which must become a standard work of reference in this specialized subject and a spur to further achievement in the field of basic research in dermatology A J G

Atlas of Skin and Venereal Diseases By W Frieboes and W Schoenfeld 2nd ed 1955 Pp 292, 476 illus G Thieme, Stuttgart (DM 118, £10)

This Atlas is finely produced but is, as books of this kind tend to be, rather expensive Nearly all of its many illustrations are in colour and they provide a vivid impression of the lesions depicted, their colours are, as a rule, as correct as the present stage of colour photography permits Each section of the book is introduced with a short chapter, dealing mainly with differential diagnosis, the pictures are adequately captioned All the common skin diseases are amply illustrated and so also are many of the less common diseases

The section on venereal diseases includes altogether 74 illustrations Primary secondary, late benign, and congenital syphilis are dealt with in 61 pictures, and there are also two illustrations of the Luotest reaction In the preface the authors mention the decline in incidence of early and of congenital syphilis They omit altogether the muco-cutaneous lesions of congenital syphilis—only the late stigmata are shown—but reproduce still a considerable number of pictures showing the pustular, rupial, and ecthymatous exanthems of acquired syphilis One has the feeling that these pictures are of historical interest only, because these types of rashes seem to have disappeared completely, they had become rare even before the present era Some of the five complications of gonorrhoea depicted are also of historical interest only (at least one hopes so), *e g*, the far advanced stage of ophthalmia and the gangrene of a testicle Keratodermia blennorrhagica and the skin eruptions which sometimes accompany Reiter's disease are not shown Six illustrations deal with ulcus molle and lymphogranuloma inguinale and eleven with non-venereal genital lesions A F

ABSTRACTS

This section of the JOURNAL *is published in collaboration with the two abstracting Journals,* ABSTRACTS OF WORLD MEDICINE *and* OPHTHALMIC LITERATURE, *published by the British Medical Association The abstracts are divided into the following sections Syphilis (Clinical, Therapy, Serology, Pathology, Experimental), Gonorrhoea, Non-Gonococcal Urethritis and Allied Conditions, Chemotherapy, Public Health and Social Aspects, Miscellaneous After each subsection of abstracts follows a list of articles that have been noted but not abstracted All subsections will not necessarily be represented in each issue*

SYPHILIS (Clinical)

Early Syphilitic Hepatitis RAJAM, R V, and RANGIAH, P N (1954) *Indian J venet Dis*, **20**, 83 3 figs, 13 refs

It is considered logical to assume that in early syphilis the liver will be invaded by *Treponema pallidum* in vast numbers, which may result in clinical or "sub-threshold" asymptomatic hepatitis The literature contains few references to the changes in the liver in the early stages of syphilis, but the authors cite the finding by Hausman of multiple, diffuse, interacinar, miliary granulomata, and that by Wagner and others of abnormal zinc sulphate turbidity reactions In a few cases there is clinical evidence of hepatic dysfunction, with enlargement of the organ and jaundice The estimated incidence of clinically manifest early syphilitic hepatitis is variable but low, being less than 1 per cent

The authors discuss three types of early syphilitic disease of the liver—early acute benign hepatitis, 'hepato-recurrence", and chronic interstitial pericellular cirrhosis of prenatal infantile syphilis—and describe three cases representative of each of the three types

It is suggested that routine needle biopsy of the liver and liver function tests in early syphilis would provide information on the frequency of asymptomatic hepatic damage *Douglas J Campbell*

Transfusion Syphilis and its Importance in Blood-bank Organization (Die Transfusionslues und ihre Bedeutung fur das Blutspendewesen) AMMON, G (1954) *Z Haut- u GeschlKr*, **17**, 216 1 fig, 40 refs

In his work at the Berlin Blood Transfusion Service the author has encountered, among a total of some 16,000 blood donors examined in the last 3 years 63 whose blood gave a strong positive reaction for syphilis This represents an incidence of 0 4 per cent (More recently, owing to the influx of refugees from eastern Germany and their occasional use as donors, this figure has probably risen to 2 or 3 per cent) It was noted in one case that as early as 7 days after the primary syphilitic infection of a donor his blood infected the recipient, the former developing a chancre 20 days later and the latter *syphilis d emblee* 4½ weeks later

The author then describes his personal investigation of 88 cases of transfusion syphilis, of which 30 per cent were due to the use of 'occasional' donors (usually relatives), in 28 per cent the donor was symptomless, the disease being in the incubating or latent stage, and in 9 per cent technical faults were responsible, in four of the cases syphilis actually being transmitted from the recipient to the donor Transfusion syphilis is a *syphilis d'emblee* without primary lesions, and its incubation period is from 1 to 3½ months The affected patient should be informed of the accident at once and treated even before it is certain that the disease has been transmitted When fresh blood is used absolute prevention is impossible, but in all cases a clinical examination of the donor including the genitalia, should be made Highly sensitive tests like the Chediak reaction or the cardiolipin flocculation test may reveal the presence of latent syphilis In the author's opinion the addition of oxide of arsenic to fresh blood does not solve the problem, and moreover has been shown to produce haemolysis on storage, if this method is adopted it should be carried out 10 min before the blood is used Perhaps the safest method is to store the blood for 72 hrs at a temperature between 2° and 4° C *Ferdinand Hillman*

Significance of the Unilateral Argyll Robertson Pupil Part II A Critical Review of the Theories of its Pathogenesis APTER, J T (1954) *Amer J Ophthal*, *38*, *209* 2 figs, bibl

In this comprehensive review of the literature dealing with the pathogenesis of the Argyll Robertson pupil, presented from the Northwestern University School of Medicine, Chicago, the author points out that the inability of experimental lesions in the central nervous system to produce a pupil which is permanently miotic as well as inactive to light, the failure to demonstrate such a lesion histologically in the central nervous system of patients with neurosyphilis, and the difficulty in explaining the miosis of a unilateral Argyll Robertson pupil all combine to lead to the conclusion that the causative lesion must lie outside the central nervous system

Strong evidence in favour of an iridopathogenesis as advanced by Langworthy and Ortega (*Medicine*, 1943, 22, 287) is provided by the reported results of clinical and histological examinations which have shown the presence of an abnormal iris in every case presenting the Argyll Robertson syndrome, by the findings of a colloidal-gold concentration curve in the aqueous humour of a paretic patient with Argyll Robertson pupils similar to that in

the spinal fluid of neurosyphilitic patients, and by the high incidence of unilateral Argyll Robertson pupil (thirteen out of 46 cases of neurosyphilis) previously reported by the present author (*Amer J Ophthal*, 1954, 38, 34) In her opinion such a high incidence is incompatible with a pathogenesis based on a lesion in the central nervous system

Summing up these various findings the author postulates that in neurosyphilis the blood vessels of the iris undergo the same pathological changes as the vessels in the dorsal nerve roots and optic nerve, there is partial occlusion and consequent undernourishment of the tissues, and this, by causing the nerves of the iris to atrophy, results in a small, immobile pupil The overactive response of the Argyll Robertson pupil to accommodation is explained on the basis of the Helmholtz theory of normal accommodation When the ciliary body contracts, the forward movement of the root of the iris causes the whole iris to move centripetally, resulting in constriction of the pupil which is purely mechanical in origin *Edward Lyons*

Ocular Manifestations of Syphilis COWEN, P H (1954) *Clin Rep Alfred Hosp Melbourne*, 4, 56

Part of a general summary is given showing the reduction in the incidence of syphilis Only thirteen cases of ocular syphilis were diagnosed at the ophthalmic clinic between 1949 and 1954 despite the attendance of thousands of patients *Ronald Lowe*

Case Report of Interstitial Keratitis of the Second Unaffected Eye 17 Years after the Affection of the First Eye RAJAM, R V (1954) *Indian J Vener Dis*, 20, 162 2 refs

Factors leading to Development of Late Manifestations of Syphilis THOMAS, E W SHAFER, J K, ZWALLY, M R, and PRICE, E V (1954) *Amer J Syph*, 38, 531 3 figs, 4 refs

Syphilitic Spinal Amyotrophy (Amiotrofia espinal sifilitica) CURCIO, F I (1954) *Pren med argent*, 41, 3449 2 figs, 10 refs

Unusual Case of Juvenile G P I ESPIR, M L E, WHITTY, C W M (1955) *Brit med J*, 1, 582 4 refs

Pulmonary Syphilis SARMA, A V S (1955) *Antiseptic*, 52, 45 5 figs, 3 refs

Syphilis in Calcutta GREVAL, S D S (1954) *Calcutta med Rev*, 21, 316 16 refs

SYPHILIS (Therapy)

Long-term Studies of Results of Penicillin Therapy in Early Syphilis SHAFER, J K, USILTON, L J and PRICE E V (1954) *Bull Wld Hlth Org*, 10, 563 4 figs, 2 refs

The authors describe an investigation carried out by the Division of Venereal Disease of the U S Public Health Service to evaluate the long-term results of the treatment of syphilis with penicillin At each of eleven treatment centres, beginning in 1945, a group of patients was selected for intensive post-treatment observation, the basis of selection being the probability that observation could be maintained in each case for at least 5 years Out of 1,570 patients so selected during a 6-year period, 1,336 (85 1 per cent) remained under observation, while 29,884 (89 4 per cent) of the 33,441 examinations scheduled were carried out, an average of nineteen per patient Since the results of treatment in this group were almost identical with those in a group of patients followed up by routine methods (42 to 64 per cent complete) it is concluded that the outcome in patients who did not complete the full period of observation was the same as in those remaining under observation

One series of 679 patients with secondary syphilis were treated with penicillin alone in a total dosage of 1 5 to 4 8 mega units (average 3 2 mega units), while another series of 292 patients with secondary syphilis were treated with arsenoxide (maximum total dosage 300 mg) and bismuth (total dosage 600 mg) in addition to penicillin (total dosage 1 2 to 4 8 mega units) The cumulative retreatment rate for 554 patients treated with penicillin alone was 13 7 per cent at 2 years and 16 3 per cent for 157 patients at 5 years, while after treatment with penicillin, arsenic, and bismuth the rate was 16 per cent at 2 years for 269 patients and 17 4 per cent at 5 years for 159 patients It is concluded that the use of arsenic and bismuth does not enhance the effect of penicillin given alone The results of treatment of early syphilis with penicillin were clearly superior to those obtained with arsenic and bismuth A minimum of 4 8 mega units penicillin is recommended for treating early syphilis *Eric Dunlop*

Treatment of Early Infectious Syphilis with N N'-Dibenzylethylenediamine Dipenicillin G A Second Report SHAFER, J K, and SMITH, C A (1954) *Bull Wld Hlth Org*, 10, 619 2 figs, 3 refs

The authors report the results of the treatment of 196 cases of dark-ground-positive early syphilis with a single injection of 2 5 mega units N N'-dibenzylethylenediamine di(benzylpenicillin) ('bicillin", benzathine penicillin) at three treatment centres cooperating with the Division of Venereal Disease of the U S Public Health Service Follow-up was short, all but 26 cases being observed for less than 18 months after treatment In cases of secondary syphilis the cumulative retreatment rate after 21 months was 4 1 per cent with benzathine penicillin as against 14 2 per cent after a single injection of 2 4 mega units procaine benzylpenicillin with 2 per cent aluminium monostearate (PAM), and 5 1 per cent after a single injection of 4 8 mega units PAM The authors conclude that a single injection of 2 5 mega units of benzathine penicillin is as effective as one of 4 7 mega units PAM *Eric Dunlop*

Results of Treatment of Syphilis with Penicillin Alone (Ergebnisse alleiniger Penicillinbehandlung der Lues) HAENSCH, R (1954) *Hautarzt*, 5, 470

The author reports the clinical and serological results

of a 3-year follow-up study of 174 patients with secondary and tertiary syphilis treated at the Municipal Skin Clinic, Wuppertal, Germany In 37 cases the patient had had no previous treatment, while the remaining 137 had been treated with a combination of arsenic and bismuth

Out of sixteen patients with secondary syphilis, who were given a total dose of either 6 or 9 mega units of a depot preparation of penicillin in doses of 400,000 or 600,000 units daily, 15 became sero-negative and remained so for 3 years No case of clinical or serological relapse occurred in this group Of seventeen patients with latent syphilis treated with a total of 6 mega units of penicillin, five defaulted immediately, ten were followed up over a period of 2 years, and eight for 3 years The author had the impression (based apparently on serological tests) that the dose of 6 mega units was too small, and most of the patients in this group were therefore given further doses totalling 9 mega units 6 months later, making 15 mega units in all In the serological tests titres were not determined, the results being reported merely as positive, doubtful positive, and negative Of the eight patients observed up to 3 years, three showed clinical improvement and five were sero-negative One of these patients relapsed serologically 1 year after treatment, but after further penicillin treatment became sero-negative and remained so for the remaining 2 years of observation

[The group of 137 patients who had previously received arsenic and bismuth is of little interest because the stage of their disease is not specified, although a vague statement is made that most of them were in the secondary stage when treatment with heavy metals was begun The exact doses of these, however, are not given The author claims that his results agree in general with those reported in the American and German literature] *R D Catterall*

Treatment of Syphilitic Meningitis (Die Behandlung luischer Meningitiden) GRUTER, W, and EHRHARDT, H (1954) *Munch med Wschr*, 96, 1343 3 figs, bibl

The authors review the present position regarding the treatment of syphilitic meningitis in the light of their own experience at the University Neurological Clinic, Marburg, and of reports in the literature Briefly, they conclude that penicillin is superior to the older methods of treatment with metallic salts The minimum total dose of penicillin recommended is 9 to 10 mega units, and this is best given in single intramuscular injections of 600,000 units of depot penicillin daily If the condition of the patient permits, a few injections of bismuth should precede the administration of penicillin in order to avoid the Herxheimer reaction In their view additional fever therapy is not advisable as it introduces dangers of its own without materially benefiting the patient If the cerebrospinal fluid shows evidence of inflammatory changes within 6 to 9 months after the initial treatment a further similar course of penicillin is given As an alternative, in the rare cases which are allergic or resistant to penicillin the older metallotherapy, together with a broad-spectrum antibiotic such as aureomycin, is recommended Three representative case histories are given *G W Csonka*

Topical Cortisone in the Treatment of Syphilitic Interstitial Keratitis Preliminary Report of Twenty Cases (26 Eyes) HORNE, G O (1954) *Brit J Ophthal*, 38, 669 5 refs

To emphasize the value of the topical application of cortisone in syphilitic interstitial keratitis the author describes twenty cases (26 eyes) so treated at the General Infirmary, Leeds He states that the three principal criteria on which assessment of results should be based are

(1) immediate effect on inflammation,

(2) duration of individual attacks and incidence of relapses,

(3) the final visual acuity

Drops of a suspension of cortisone acetate (5 mg per ml) were given to all the patients, who received at the same time systemic treatment for syphilis—penicillin, with or without bismuth The observation period was over a year in the majority of cases

There was rapid relief of symptoms with restoration of normal vision in nearly all the cases In some the improvement was slower, the rate being influenced by the duration of the disease before treatment started and by the dosage of cortisone Adequate dosage appeared to shorten attacks Relapses were well controlled, but the author considers that the series is too small and the period of observation too short to assess the frequency of relapses Final visual acuity in this series was considered to be much superior to that obtained in other reported series, in only three eyes was visual acuity less than 6/12 No contraindication to the use of cortisone was noted

[The author does not define an "adequate dosage" of cortisone, nor does he emphasize sufficiently that in the long-standing case cortisone may act much more slowly and cannot be expected to remove established fibrosis A more detailed report, which is promised, would be valuable] *Robert Lees*

Question of Penicillin in the Treatment of Neurosyphilis I Problems and General Considerations (La questione della terapia penicillinica nella neurolue I Problemi e direttive generali) CALLIERI, B (1954) *Clin terap (Roma)*, 7, 525 Bibl

Prenatal Penicillin Prophylaxis against Congenital Syphilis (Sulla profilassi penicillinica prenatale della sifilide congenita) SCAGLIONE, G, and ROSSI, S (1954) *Aggiorn pediat*, 5, 857 21 refs

Cure of Syphilis in the Light of the Treponemal Immobilization Test of Nelson and Mayer (Die Heilung der Syphilis im Lichte der Reaktion nach Nelson und Mayer) KOGOJ F (1955) *Wien med Wschr*, 105, 11

SYPHILIS (Serology)

The Treponemal Immobilization (TPI) Test of Nelson Its Importance in the Diagnosis and Understanding of Human Syphilis as Judged from Personal Experience (La prueba de inmovilizacion treponemica de Nelson (TPI) Su interes diagnostico y doctrinal en la sifilis

humana, seguida de un comentario derivado de neustra experiencia personal) VILANOVA, X (1954) *Act dermo sifiliogr (Madr)*, **46**, 3 4 figs

The author reviews the development of serological tests for syphilis, including the treponemal immobilization (TPI) test of Nelson and Mayer, and discusses the results obtained with this test during the past 18 months in the School of Dermatology of the University of Barcelona

The value of the test was confirmed, although it was found to be less sensitive than the standard serological tests in cases of early secondary syphilis, the reaction being negative in eleven out of 31 such cases On the other hand in a series of 29 cases of neurosyphilis the TPI reaction was positive in the blood in every case in which the cerebrospinal fluid showed specific change, a finding of particular value in that it will enable lumbar puncture to be avoided in many cases Amongst his other conclusions the author considers that a negative TPI reaction rules out the presence of syphilis (or other treponematosis) except in the case of infections of less than 3 months' duration or congenital disease in an infant of less than 3 months In treated syphilitics negativity of the TPI reaction, together with the other clinical findings, is an important factor in the determination of cure

[No references are given to the many authorities cited in the text] *Eric Dunlop*

***Treponema pallidum* Immobilization Test in the Evaluation of Patients with Positive Serologic Tests for Syphilis** KERN, A B (1954) *New Engl J Med*, **251**, 807 5 refs

Writing from the U S National Naval Medical Center, Bethesda, Maryland, the author makes a plea for the wider use of the treponemal immobilization (TPI) test, pointing out the potential danger to the patient's future of failure to diagnose syphilis because of a negative result of the more common reagin tests, or on the other hand the unnecessary hardship which may be caused by accepting a biologically false positive reaction as evidence of syphilitic infection Brief histories of seventeen typical cases in which the TPI test confirmed or refuted a doubtful diagnosis of syphilis are presented

The immobilizing antibody occurs only in syphilis and closely related treponemal infections, namely, yaws, bejel, and pinta It usually lags behind reagin in appearance and disappearance, it may not appear in early cases which have been adequately treated, and it usually does not disappear from the serum in long-standing cases, whether treated or not Thus it may give a false negative result in an early case, on the other hand a positive test result—like the Mantoux reaction in tuberculosis—shows only that the patient has had a syphilitic infection at some time The progress of the disease must then be judged from the clinical course and from repeated quantitative reagin tests a positive TPI reaction does not necessarily indicate the need for treatment The immobilization test is of most use in the differentiation between false positive reagin test results and latent syphilis It is valuable also in that it remains positive in untreated cases of neurosyphilis, cardiovascular and congenital syphilis, and of gumma Unfortunately the test is complicated and difficult to perform, requires expensive materials and trained personnel, and to the author's knowledge is at present carried out at only eleven laboratories in the United States (a list of these is given) It is urged in conclusion that this useful test should be made more widely available

Ferdinand Hillman

Specificity of the Treponemal Immobilization Test ZELLMANN, H E (1954) *Amer J Syph*, **38**, 506 14 refs

The *Treponema pallidum* immobilization (TPI) test was carried out at Johns Hopkins Hospital, Baltimore, on 45 normal persons and on 110 patients with diseases other than syphilis Apart from four cases in which the test was "unsatisfactory", all the results were negative except for a doubtful reaction in a case of disseminated sclerosis and a positive reaction in a case of paroxysmal auricular fibrillation Neither of these patients showed any other evidence of syphilis, and the results of the standard tests for syphilis (STS) were negative in both instances As it was not possible to obtain second specimens of serum for confirmation it is not known whether these were false positive reactions or resulted from errors in technique These cases, together with others reported in the literature, total to one doubtful and three positive reactions to the TPI test among 1,397 presumed non-syphilitic sera tested, representing a possible incidence of non-specific reactions of 0 3 per cent

Further tests were carried out on sera from 441 patients with clinically verified syphilis drawn from private practice who had been treated by various methods 1 to 40 years previously The TPI reaction was positive in 24 and negative in 44 cases of treated early syphilis, and positive in 351 out of 372 patients with treated late symptomatic syphilis The TPI-negative cases in this group included patients with tabes (five), other forms of neurosyphilis (five), and late congenital syphilis (three) It is therefore concluded that in treated late syphilis with very few exceptions the immobilizing antibody, unlike reagin, persists in the serum indefinitely regardless of the antisyphilitic treatment given, whereas in treated early syphilis it may disappear The immobilizing antibody similarly persists in treated congenital syphilis, and although its behaviour in latent syphilis has not been studied, it is reasonable to suppose that it persists also in cases of late latent syphilis (of more than 4 years' duration) despite treatment It is therefore considered that provided treated early syphilis can be excluded and there is no clinical evidence of late syphilis (especially tabes and congenital syphilis) a negative TPI reaction, confirmed by repetition on the same specimen of serum, can be used to differentiate between syphilitic infection and the biological false positive phenomenon, regardless of any treatment which may have been given

[This paper gives a most useful survey of the results of TPI tests at various stages of syphilis gathered from the principal series so far reported in the literature] *A E Wilkinson*

Agglutination of Pathogenic *Treponema pallidum* by Syphilitic Serum (Sulla reazione di agglutinazione fra siero di sifilitico e *Treponema pallido* patogeno) DARDANONI, L (1954) *Ri Ist sieroter Ital*, **29**, 440 6 figs, 20 refs

After a brief review of the literature concerning antitreponemal antibodies, the author describes his experience at the Institute of Hygiene of the University of Palermo with the *Treponema pallidum* agglutination test as performed by the technique of McLeod and Magnuson (*Publ Hlth Rep (Wash)*, 1953, **68**, 747, *Abstracts of World Medicine*, 1954, **15**, 212) It is assumed that the treponemal agglutinating antibody in syphilitic serum is identical with the immobilizing antibody of Nelson

The rabbits used for testicular culture were given a dose of x rays on the day before inoculation, and fresh bovine serum was used as conglutinin Sera from two healthy subjects and six patients with syphilis were used, one of the latter, from a patient with a gumma, giving a negative response to the immobilization (TPI) test of Nelson and a weak positive result with the agglutination test The procedure is described, and photographs are reproduced to show negative and positive agglutination and to illustrate the annotation used (+ to ++++) for recording the results, both the presence of clumps and the absence of free treponemes being used as indices of positivity

The results proved difficult to read—only in control tests in which both the patient's serum and the bovine serum were replaced by saline was there no agglutination at all, an increase in the size of the agglutinate was not always associated with a decrease in the number of free single treponemes, and positive sera produced some agglutination even in the absence of complement The use of an initial suspension of ninety treponemes per dark field (as opposed to thirty in the original technique) made no material difference to the results

It is concluded that since the occurrence of autoagglutination in the treponemal suspension makes both qualitative and quantitative evaluation of the results uncertain, the treponemal agglutination test, which is delicate and costly to carry out, has not yet reached a sufficiently mature stage of development to warrant its use as a substitute for the TPI test

Ferdinand Hillman

Frozen Syphilomatous Rabbit Testes as Source of *Treponema pallidum* for the Immobilization (TPI) Test for Syphilis ANDERSON, R I, KENT, J F, and SANDERS, R W (1954) *Amer J Syph*, **38**, 527 3 refs

This report from the Walter Reed Army Medical Center, Washington, D C, extends the observations of Chorpenning and others (*Amer J Syph*, 1952, **36**, 401, *Abstracts of World Medicine*, 1953, **13**, 113) on the use of syphilomatous testes preserved at −55° to −45° C as a source of treponemes in the treponemal immobilization (TPI) test A total of 185 testes were harvested and stored in the frozen state for varying periods—91 for 1 to 7 days, 83 for 1 to 12 weeks, and eleven for 3 to 18 months On thawing and extraction with the basal medium used in the test the average motility of the organisms was 90 per cent, while the average motility of treponemes extracted from 198 unfrozen testes was 97 per cent The suspensions from the frozen testes were uniformly satisfactory when incubated under test conditions (18 hours at 35° C) The proportion of motile organisms recovered from the testes stored for the maximum period of 18 months was little different from that from testes stored for short periods, and the slightly lower motility compared with that of treponemes from fresh testes appears to be related to damage inseparable from the processes of freezing and thawing rather than to the duration of storage in the frozen state

By means of a special container refrigerated by solid carbon dioxide, frozen syphilomatous testes have been sent by air mail to centres as far from Washington as Germany and Cuba On receipt, treponemes from these testes have been successfully used to establish syphilitic infection in rabbits *A E Wilkinson*

Anticomplementary Serum in Modern Modified Wassermann Reaction KARIM, M A (1954) *Indian J Vener Dis*, **20**, 160

Preparation of Amboceptor and its Titration in Wassermann Reaction KARIM, M A (1954) *Indian J Vener Dis*, **20**, 161 2 refs

Filter Paper Test in the Diagnosis of Syphilis KARIM, M A (1954) *Indian J Vener Dis*, **20**, 159

Problem of the Reaction between Antibody and Complement in the Wassermann Reaction carried out with Cardiolipin (Zur Frage des Bindungsverhaltnisses Antikorper Komplement bei der mit Cardiolipin ausgefuhrten WaR) RUGE, H (1954) *Z Hyg InfektKr*, **140**, 163 3 figs, 7 refs

Combating of V D in Denmark with Special Reference to the Tests performed at the Staten Seruminstitut, Copenhagen REYN, A (1954) *Calcutta med Rev*, **21**, 320 13 refs

SYPHILIS (Pathology)

Electron-microscopical Examination of Reiter's Spirochaetes and Nichols's Treponemes (Elektronen mikroskopische Untersuchungen an Reiter-Spirochaetales und Nichols-Treponemen) SCHMEROLD W and DEUBNER, B (1954) *Hautarzt*, **5**, 511 9 figs, 10 refs

The authors have examined specimens of the Nichols strain of treponeme and of the Reiter spirochaete under the electron microscope at the University of Munich, and here describe their findings, several beautifully clear electron micrographs being reproduced in the text They draw attention to the fibrils which are clearly seen in most of the pictures attached to one or other end of the body of the organism, and which in certain specimens are arranged in bundles running the whole length of the body They support the conclusion reached by Bradfield and Cater (*Nature, Lond*, 1952 **169** 944 *Abstracts of World Medicine*, 1952, **12**, 394) that the fibrils are

contractile and are probably responsible for the spiral form of the spirochaetes, and suggest that the flagellum-like fibrils described above had been partially detached from the bundles by the destructive effect of the various means of preparation used The various possible ways in which the fibril bundles may play a part in the movements of the organisms are discussed, with illustrative sketches [The electron micrographs reproduced are outstanding in their clarity and definition]

R D Catterall

Improved Methods for Demonstrating Acid-fast and Spirochetal Organisms in Histologic Sections BEAMER, P R, and FIRMINGER, H I (1955) *Lab Invest*, 4, 9 3 figs, 7 refs

SYPHILIS (Experimental)

Electrophoretic Studies in Experimental Syphilis in Rabbits (Elektrophoresestudien bei der experimentellen Kaninchensyphilis) KUMMEL, J (1955) *Arztl Wschr*, **10**, 58 3 figs, 15 refs

GONORRHOEA

Further Observations on Streptomycin Treatment of Gonococcal Infection (Ulteriori osservazioni sulla terapia streptomicinica nell'infezione gonococcica) CHIARENZA, A (1954) *G ital Derm Sif*, **95**, 381

The author reported 3 years ago that of a series of 421 patients with gonorrhoea who were treated with two doses of 250 mg streptomycin given intramuscularly, 419 were cured He now reports that of a new series of thirty patients treated in the same way at the Venereological Clinic of the University of Catania, only 22 were cured with the above dosage, three requiring a total dose of 750 mg and five being resistant to treatment The five streptomycin resistant patients included two of the five who had previously been treated with the drug and three of the remaining 25, none of whom had received streptomycin previously Whereas in the former series gonococci had disappeared from the discharge within 2 hours of the first injection, it took 4 to 5 hours in the present series to eliminate them Subjective symptoms disappeared rapidly in all cases The resistant cases responded to treatment with penicillin and sulphonamides

Ferdinand Hillman

Observations on the Applied Epidemiology of Gonorrhoea ANDERSON D O, and NELSON, A J (1954) *Canad J publ Hlth*, 45, 381 2 figs, 2 refs

In the Province of British Columbia between 1946 and 1953 the number of reported cases of infectious syphilis fell by 97 per cent, whereas the corresponding figure for gonorrhoea was only 36 per cent Gonorrhoea, therefore, is now considered the major problem in the control of venereal disease In this paper from the British Columbia Department of Health and Welfare, Vancouver the authors review present and past thinking regarding the epidemiology of gonorrhoea, and describe a recently introduced control programme for the City of Vancouver which is based on the fact that a large number of the male cases seen were most probably the result of contact with a comparatively small number of infected women who either did not know they had gonorrhoea or made no effort to have it treated and thus formed a reservoir of infection sometimes for indefinite periods A successful epidemiological attack must therefore be based on the recognition and elimination of this reservoir In essence, this means that the infected, untreated women must be identified through their recent male contacts and brought to treatment in as short a time as possible if the best results are to be achieved

Arising from these considerations a four-point programme has been instituted, as follows

(1) Intensive interviewing of all males coming for treatment regarding their female contacts during the 6-day period preceding the onset of symptoms

(2) Attempts made to locate all identifiable female contacts within 24 to 48 hours

(3) Immediate treatment for gonorrhoea, irrespective of bacteriological findings, of all female contacts located

(4) An effort made to enlist the cooperation of proprietors and managers of so-called hotels in the city where many of the promiscuous contacts take place

The results of this programme, after 6 months of operation, are considered encouraging but since 42 per cent of all patients with venereal disease in this area are first seen by a private physician, the enlistment of his cooperation too in the tracing of contacts is an urgent necessity

Benjamin Schwartz

NON-GONOCOCCAL URETHRITIS AND ALLIED CONDITIONS

Abacterial Urethritis a Report of Eight Cases with Isolation of the Pleuropneumonia-like Organism HOLLIS, W J (1954) *J Urol (Baltimore)*, 72, 671 8 refs

At the U S Air Force Hospital, Barksdale, Louisiana, over a 27-month period, 179 cases of gonococcal urethritis were encountered, as compared with seventeen cases of urethritis due to pleuropneumonia-like organisms (PPLO), six cases of non-venereal urethritis of unknown origin, and one case of bacterial urethritis Of the seventeen cases due to PPLO, eight for whom sufficient information was available are described in detail Three of these cases occurred soon after the treatment of gonorrhoea and one case 5 months after such treatment A fifth patient admitted sexual contact 2 months previously, but the remaining three denied such contact The authors claim that these observations suggest a venereal transmission of the disorder Of four of the patients treated with streptomycin alone (in doses of 5 to 9 g for 5 to 9 days), all showed a good response The other four cases were treated with a combination of streptomycin and sulphadiazine and also showed good response, and it is suggested that this was due mainly to the streptomycin and not to the sulphadiazine

R R Willcox

Skin Tests for Lymphogranuloma Venereum in Non-Specific Urethritis (In English) WILLCOX, R R (1954) *Acta derm-venereol (Stockh)*, 34, 430 1 fig, 2 refs

This paper forms part of a series describing an investigation to ascertain whether patients suffering from so

called non-specific urethritis react to the antigens of viruses of the lymphogranuloma-psittacosis group (One of the series has already been published (Macrae and Wilson, *Brit J venet Dis*, 1953, **29**, 231, *Abstracts of World Medicine*, 1954, **15**, 475), a second is in the press) In the present paper the author describes the results of the Frei test, carried out at St Mary's Hospital, London, or King Edward VII Hospital, Windsor, on 84 patients suffering from non-specific genital infections and 62 controls attending the venereal disease clinics for other reasons Two preparations of antigen were used —a vaccine made in Britain and a commercial product, "lygranum", made in the United States The results of the tests were read at 48 hours, a positive result being recorded when an inflammatory papule more than 6 mm in diameter developed on the test arm but not on the control arm A papule 5 to 6 mm in diameter was interpreted as a 'doubtful" positive reaction, and a papule less than this in diameter as a negative reaction The results appeared to be similar with the two vaccines Positive reactions were obtained in 13 1 per cent of cases of "non-specific" infection compared with 4 8 per cent of the controls In the former group there did not appear to be any relationship between the incidence of positive and doubtful reactions and activity or duration of the infection It was concluded that it was not possible to establish any relationship between "non-specific" genital infection and reactivity to Frei antigen

A J King

Epidemiological Position of Non-Gonococcal Urethritis in Italy (La situazione epidemiologica delle uretriti non gonococciche in Italia) MIDANA, A, and SERRI, F (1954) *Minerva derm* (*Torino*), **29**, 399 1 fig, 27 refs

New Etiologic Agent in Non-Specific Vaginitis GARDNER, H L, and DUKES C D (1954) *Science*, **120**, 853

CHEMOTHERAPY

Tetracycline in the Treatment of Certain Venereal Diseases MARMELL, M, and PRIGOT, A (1954) *Antibiot and Chemother*, **4**, 1117 7 refs

Tetracycline hydrochloride was given by mouth to 115 patients with gonorrhoea (68 of whom were adequately followed up), two with lymphogranuloma venereum, and five with chancroid at the Harlem Hospital, New York Two dosages of tetracycline were used in the treatment of the patients with gonorrhoea—namely, 500 mg 6-hourly to a total of 1 5 g and 500 mg followed at 6-hourly intervals by 250 mg to a total of 1 g Of the fifty patients followed up who had received the larger dosage, 49 were cured, of the eighteen patients followed up who received the smaller dosage, sixteen were cured The patients with lymphogranuloma venereum and chancroid received 1 g tetracycline daily until the lesions were healed Both of the patients with lymphogranuloma venereum responded favourably and the lesions healed after 10 to 11 g had been given There was a similar favourable response in all five cases of chancroid, the lesions healing after administration of 10 to 21 g

No untoward side-reactions were noted in any of these cases

R R Willcox

PUBLIC HEALTH AND SOCIAL ASPECTS

Can Pre-employment Serologic Tests for Syphilis be Justified? GRAHAM, R M (1955) *Industr Med Surg*, **24**, 73

Some Aspects of the Epidemiology of Syphilis CLARK, E G (1954) *Calcutta med Rev*, **21** 301 22 refs

Role of the Public Health Program in Venereal Disease Control CUTLER, J C (1954) *Calcutta med Rev*, **21**, 293

Venereal Disease Control Programme—India TAMPI, R B (1954) *Calcutta med Rev*, **21**, 288

Regulations Governing the Official Campaign against the Venereal Diseases in Spain (Normas que regulan la Lucha oficial contra las enfermedades venéreas) (1954) *Act dermo-sifiliogr* (*Madr*), **3**, 216

MISCELLANEOUS

Vaginal Discharges and Trichomoniasis BHARADWAJ B M (1954) *Indian J venet Dis*, **20**, 153 12 refs

Skin and Venereal Warts and Their Treatment SAHU, K C (1954) *Indian J venet Dis*, **20**, 146

Minor Venereological Affection (Sur les affections venereologiques mineures) DUREL, P, BARAN, L R, and HARDY, L (1955) *Rev Prat*, **5**, 489 13 refs

Venereal Diseases in England LAIRD, S M (1954) *Calcutta med Rev*, **21**, 311 10 refs

Lymphogranuloma Venereum in Egypt MIKHAIL, G R (1954) *J Egypt med Ass*, **37**, 895 17 refs

Treponematoses Programme of the World Health Organization Changing Concepts in the Epidemiology and Control of the Treponematoses and Special Activities in South-East Asia GUTHE, T, and WILLCOX, R R (1954) *Calcutta med Rev*, **21**, 250 7 figs, 23 refs

Other Treponematoses Control Activities of the World Health Organization WILLCOX, R R, and GUTHE, T (1954) *Calcutta med Rev*, **21**, 275 3 figs, 15 refs

EDITORIAL

THE TREPONEMAL IMMOBILIZATION TEST

Few will deny that interest in the treponemal immobilization (TPI) test is increasing This may well be due to the fact that, at long last, we have a serological test for syphilis which employs a specific antigen Such a test naturally gives rise to the hope that the problem of identifying non-treponemal reactors is well on the way to solution In addition to the increasing urgency of this problem (particularly when antenatal patients are involved) information has been somewhat slow to come to hand During the last few years there has been a steady stream of papers on the TPI test, but so many of these are concerned with relatively small numbers of sera from selected patients Critical reviews of the literature on this subject are few and Zellmann's* no doubt is the latest and best of these

Surprising as it may seem, relatively few sera from healthy non-treponemal patients have been tested by means of this reaction On the other hand, much attention has been devoted to the study of the results of the TPI test with sera from patients labelled as latent syphilitics Until recently, these patients were diagnosed by means of the standard serum tests for syphilis, but with the advent of the TPI test, many such diagnoses became suspect, and it is pertinent to ask if one is to accept the TPI reaction with such sera as 100 per cent specific Few workers have claimed such omniscience for any pathological test and, at this stage, the cautious may be forgiven for entertaining a degree of agnosticism whilst wondering whether those who would consign *all* serological tests for syphilis to the dustbin are not overstating their case

Be that as it may, there is no doubt that the TPI test is a most valuable addition to our methods of diagnosing syphilis, and it seems that clinicians in Great Britain are being deprived of considerable help while the present restrictions on its employment are in force

It is suggested, however, that more information concerning the test is required Of necessity, evidence is slow to accumulate This is due not only to the time factor of the technique but also to the paucity of certain types of patients (at least in Great Britain) whose sera would be suitable for investigation by means of serial testing In addition, defaulting patients and a shifting population play their part in holding up the final assessment of the test

Readers of this Journal will, therefore, we feel sure, welcome the articles in this issue recording the experiences of the two authors with this test The information contained therein will add several more pieces to the jigsaw of knowledge necessary before the TPI test finally takes its rightful place in the battery of diagnostic serological tests for syphilis

* Zellmann, H E (1954) *Amer J Syph* 38 506

Brit J vener Dis (1955), **31**, 134

STUDIES ON THE REPRODUCIBILITY AND SPECIFICITY OF THE TREPONEMAL IMMOBILIZATION TEST*†

BY

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Since its introduction in 1949, the Treponemal Immobilization Test (TPI) has become accepted as a highly specific test in the treponematoses, although the majority of published reports have dealt with its results in syphilis and in patients suspected of giving non-treponemal reactions with the Standard Tests for Syphilis (STS)

In this paper, the behaviour of the test with non-syphilitic sera is examined to establish the criteria of negativity, its specificity is considered, and the conclusions reached are applied to routine sera

Technique and Material

The methods used follow those described by Nelson and Mayer (1949) with minor modifications described by Wilkinson (1954) A further modification used at the Royal Free Hospital is the incubation of the tests in a McIntosh and Fildes Jar in an atmosphere of hydrogen 95 per cent and carbon dioxide 5 per cent after only one replacement of air with gas mixture

The sera tested came from the following sources

(*a*) Antenatal clinics of the Royal Free Hospital
(*b*) Patients attending the V D Department, Royal Free Hospital
(*c*) Patients attending the Whitechapel Clinic, London Hospital
(*d*) Patients attending the general departments of the Royal Free Hospital
(*e*) The second distribution of WHO control serum

REPRODUCIBILITY

As satisfactory reproducibility is a prime requirement of any laboratory test, this aspect is considered first Some authors (Olansky, Harris, and Hill, 1953, Saurino, 1953) have been dissatisfied with the reproducibility obtained, while Boak, Miller, and Carpenter (1954) achieved good reproducibility by duplicating the test

The TPI test is liable to technical errors like any other serological test, and therefore should always be repeated on a second specimen of serum before any decision is taken on the results of the test alone

It has, in addition, certain inherent variables that require comment First, the antigen is potentially variable in that the treponemal suspension may be partially sensitized with antibody from the rabbit used in its preparation, secondly, the sensitivity of the test is dependent on the titre of the complement used, thirdly, a further variation due to sampling error is added during the reading of the test As there is, therefore, an experimental error, it is important to know how large this error is if the results of the test are to be interpreted correctly

Results and Discussion

The general behaviour of the test under average conditions is illustrated by Fig 1, which shows the results in 1,000 consecutive patients in whom a valid result was obtained In addition, no valid result was obtained with 43 patients due to the specimens being anticomplementary, toxic to treponemes, or infected

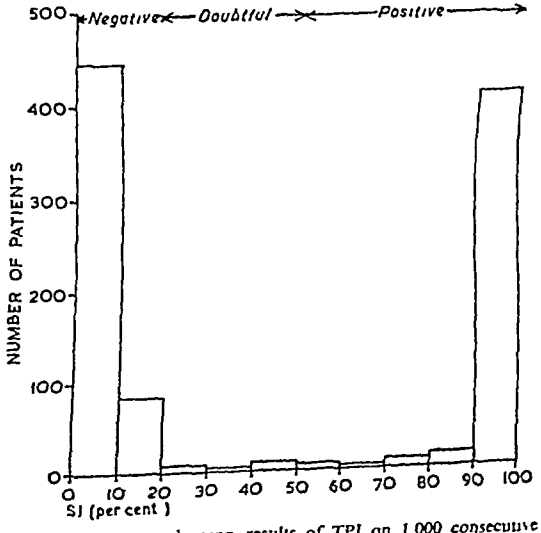

FIG 1.—Histogram showing results of TPI on 1 000 consecutive patients.

* Received for publication June 30 1955
† Based on a paper read to the M S S V D on February 25 1955

The value Specific Immobilization (SI) is obtained by substituting the percentage survival in the test and control tubes in the formula given below

$$\text{Specific Immobilization} = \frac{(C-T)}{C} \times 100 \text{ per cent},$$

where C = percentage survival in the control tube (no active complement),
and T = percentage survival in the test tube (with active complement)

Inspection of this formula shows that when the test survival is zero (*i e*, with a strongly positive serum), the SI will be 100 per cent irrespective of the control survival, while, in all other cases, the value $(C-T)$ may include the sum of the experimental errors inherent in estimating these two values

The boundaries between the negative and doubtful, and doubtful and positive zones of 20 per cent and 50 per cent SI were laid down by Nelson, Zheutlin, Diesendruck, and Austin (1950) on a basis of experience Of the 1,000 patients tested, only 22 gave results in the doubtful zone Of these, three were cases of treated primary syphilis, seven of treated secondary, four of treated latent syphilis, and seven of treated congenital syphilis The remaining case was a 14-year-old girl whose Kahn test was found to be positive at an antenatal examination She was treated with penicillin before she was referred to the Royal Free Hospital Her consort was said to be normal and her STS were negative when examined at the Royal Free Hospital

Only 33 of the 443 positive patients gave results with an SI between 50 and 90 per cent , the majority of the remainder gave an SI of 100 per cent and were probably of high titre

Among the negatives, 450 had SIs of 9 per cent or less and 83 of 10 to 19 per cent Thus among cases classed as negative, about one in six had an SI of 10 per cent or more It is therefore important, from both a theoretical and a practical point of view, to decide if these SI values in the upper part of the negative range are due to minimal amounts of antibody or to experimental error The sera used in the following study are the 320 that did not give positive results in the series of 323 antenatal patients reported later The reading technique was modified in this experiment in that the result was recorded after counting 25 treponemes instead of counting further samples if the result appeared to approach the doubtful range This modification permits a statistical analysis of the working of the test that is not possible in the majority of serological tests (Table I) These figures show the frequencies with which the indicated survivals were observed, *e g*, a test survival of 23 treponemes with a control survival of 24 treponemes occurred 25 times, and a control survival of 23 treponemes occurred in all 102 times

TABLE I

FREQUENCY TABLE SHOWING RELATION OF TEST AND CONTROL SURVIVAL IN 365 TESTS ON 320 NEGATIVE SERA*

No of Motile Treponemes	Tests 25	24	23	22	21	20	19	18	17	16	15	Total
25	3	10	7	5	4	5	1	3	—	—	—	38
24	6	19	25	7	6	8	2	3	—	—	—	76
CONTROLS 23	9	17	27	16	12	14	4	1	2	—	—	102
22	—	3	18	12	12	6	3	3	1	—	—	58
21	2	3	7	11	7	8	3	2	1	—	1	45
20	—	—	1	4	6	7	2	2	—	—	—	22
19	—	1	—	1	3	2	4	1	1	—	—	13
18	—	—	2	2	—	3	2	—	—	2	—	11
Total	20	53	87	58	50	53	21	15	5	2	1	365

Number	Tests	Controls
Mean Survival	21 8 (87 2 per cent)	22 54 (90 2 per cent)
Standard Deviation	1 95	1 78
Sample Variance		
Sampling Error	2 92	2 22
Variation in Sera or Medium	0 40	0 34
Other Causes	*0 48*	*0 62*
Total	3 80	3 18
Standard Error of Variance	*0 28*	*0 24*

* The statistics are given in terms of organisms per sample

The two causes of variation, which can be calculated from these figures, are that due to sampling error, which depends on the mean survival and the size of the sample examined, and that due to non-specific variations in the medium on different days or in the individual sera resulting in high (or low) survivals occurring together in the same test, which is calculated from the correlation coefficient * As variance is additive, the variance due to unexplained causes can be found by subtracting the variance of known causes from the observed variance This remainder will be subject to the errors inherent in the estimations of variance from which it is calculated The error in estimating the variance of the

* The correlation coefficient r is a measure of the relationship between two variables r may be of any value from -1 to -1 When $r = +1$ the variables are directly proportional to each other When $r = 0$ there is no relationship, and when $r = -1$, the relationship is inverse

In this example $r = 0\ 324$

The variance due to this correlation $= r^2 V$,
where V = the variance.

The variance due to sampling error will equal that of a similar binomial distribution and is given by the following

Variance of sampling error $= pqn$
where p = proportion motile
q = proportion non motile
n = number in sample

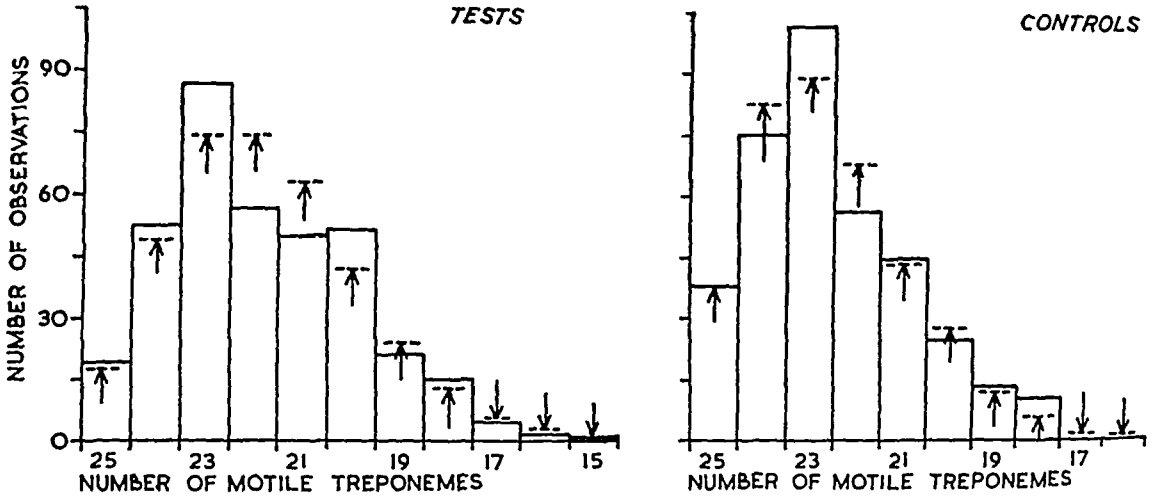

FIG 2—Histograms showing survival in tests and controls of 365 TPIs on 320 negative sera Arrows indicate predicted height of columns

sampling error is negligible The standard error of the correlation coefficient is such as to increase the standard error of the variance due to " other causes " from 0 28 (S E of variance) to 0 31 in the tests, and from 0 24 to 0 26 in the controls There is, therefore, a two-thirds chance that the variance from " other causes " lies in the range 0 17–0 79 for the tests, and 0 36–0 88 for the controls (+ or — one S E), and a 95 per cent chance that they do not exceed 1 10 and 1 14 (+ two S E) respectively Thus, in this series, there is no evidence that the tests show a greater unexplained variation than the controls that might be attributed to the presence of an immobilizing antibody in the sera examined

The lower mean survival in the tests, therefore, may be due to a steady amount of sensitization of the treponemes with antibody from the rabbits used or to a non-specific action of complement

The hypothesis that the variation observed is due to sampling error superimposed on a much smaller variation in survival in the individual tests or batches can be further examined by comparing the observed distributions with those calculated on the basis of this hypothesis (Fig 2)* There is no significant difference between these distributions (tests, $p = 0\,3$, controls, $p = 0\,5$)

If this hypothesis is accepted on the agreement between the observed and expected distributions, it would appear that the method of reading the test introduces a greater error than the variation in survival that occurs

The results of the 365 tests expressed as SIs are shown in Fig 3 † together with their expected distribution There is no significant difference between the observed and expected distributions ($p = 0\,15$) Twenty tests have SIs of 20 per cent or over against 25 predicted

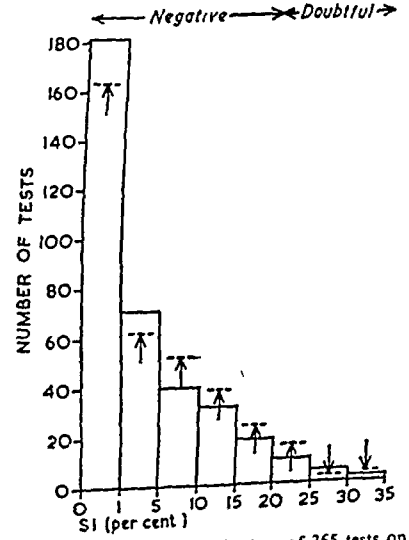

FIG 3—Results as specific immobilization of 365 tests on negative sera Arrows indicate expected height of columns

When the results of the 45 repeat tests on sera with high values of SI are averaged with the original results, the high values of SI disappear This and the final results on the 320 sera are shown in Fig 4 (opposite)

* The expected values shown in Fig 2 are modified Poisson distributions having means and variances equal to those observed

† The expected values shown in Fig 3 are derived from similar distributions but of variance equal to that of the sampling error plus the variance from other causes The expectation of each combination of survivals (e g test 92 per cent control 96 per cent) was calculated and these were grouped according to SI

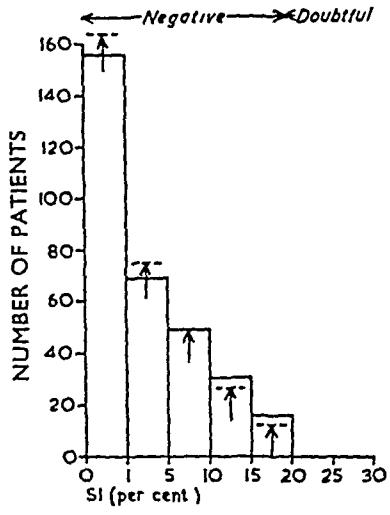

FIG 4 —Results of 320 negative sera after averaging original and repeat results Arrows indicate distribution found by Wilkinson (1954) among negative clinic cases (adjusted to same total)

The arrows indicate the distribution of SIs obtained by Wilkinson (1954) on patients attending the Whitechapel Clinic who were presumed to be non-syphilitic There is no significant difference between the two distributions ($p = 0.7$)

These results show that, with negative sera, the reproducibility of the TPI approaches the maximum possible, and that, using similar techniques, the two laboratories obtained almost identical distributions of results using sera from different sources

Sera giving doubtful results were insufficient for analysis By examination of the results of repeated quantitative examination of the same positive control serum, the best estimate of the behaviour of the TPI in this zone is obtained Suitable dilutions of the serum are set up and the SI of each is estimated From these values, the dilution that would have produced an SI of 50 per cent is estimated graphically Fig 5 shows the results obtained in the two laboratories over a period of about 10 months using the second WHO control serum A number of invalid estimations are included for comparison, those marked " C " had insufficient residual complement, and those marked " S " were discarded because of sensitization with rabbit antibody These invalid estimations fell among the lowest (C) and highest (S) titres found The invalid estimates were not included for calculation of mean titre and standard deviation

The difference between the mean titres of the two laboratories is less than half a dilution, and the standard deviation in each was between a third and a half dilution Thus, in quantitative estimations, the majority of results will fall within half a dilution of the mean value and almost all within the generally accepted range of reproducibility of one dilution The agreement between the two laboratories would also appear to be satisfactory

The mean of forty estimations of SI of the 1 in 16, 32, and 64 dilutions were 93 7, 54 8, and 20 4 per cent respectively, indicating that, where partial immobilization occurs, doubling the amount of antibody corresponds to an increase in SI of about 35 per cent

These results show that while the general degree of reproducibility is satisfactory, the variation that occurs gives results, reported in terms of SI or titres producing SI 50 per cent , a misleading appearance of accuracy unless each test is repeated several times

The conclusions reached from the laboratory aspect of the test are borne out by the results of repeat tests on the same specimen of serum and on different specimens of serum from the same patient The results of repeat tests on the same specimen of serum are shown in Table II (*overleaf*) These repeats were carried out only when the original result appeared to require checking, and they, therefore, represent the worst agreement found among the results of the 1,000 patients shown in Fig 1 The results are divided into four groups

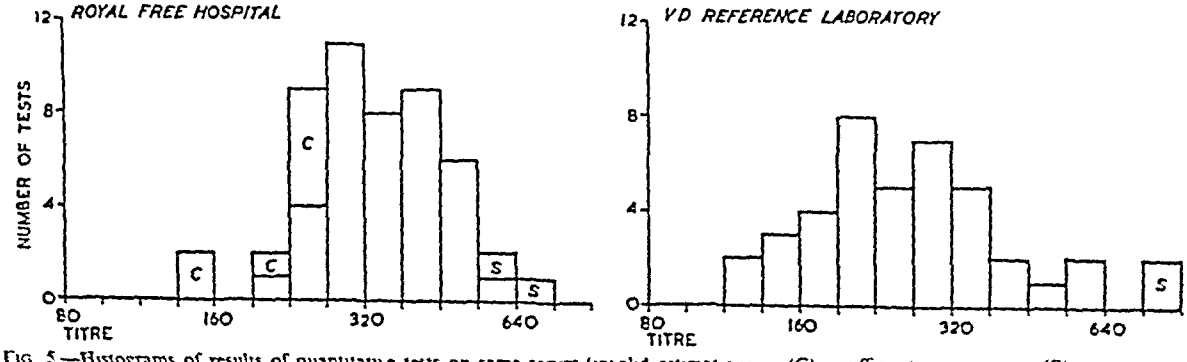

FIG 5 —Histograms of results of quantitative tests on same serum (invalid estimations (C) insufficient complement (S) sensitization)

TABLE II
RESULTS OF REPEAT TESTS ON 240 SERA SELECTED FROM THE 1,000 SHOWN IN FIG 1 REQUIRING CONFIRMATION OF RESULT

Second Test		First Test			
		Positive	Weak Positive	Doubtful	Negative
	SI	100–76	75–50	49–20	19–0
Positive	100–76	105	3	0	0
Weak Positive	75–50	3	2	3	0
Doubtful	49–20	2	5	8	9
Negative	19–0	0	0	29	71

(*i*) negative (SI, 0–19 per cent),
(*ii*) doubtful (SI, 20–49 per cent),
(*iii*) weak positive (SI, 50–75 per cent),
(*iv*) positive (SI, 76–100 per cent)

The result of the first test is shown at the top of the Table and the second at the side Among the 240 pairs of tests shown, complete agreement occurred in 186 pairs (77 5), and minor disagreement (that is, one test negative the other doubtful, one test doubtful the other weak positive, or one test weak positive the other positive) occurred in 52 pairs (21 6 per cent) of which 38 occurred between doubtful and negative and correspond to the doubtful results shown in Fig 3 A greater difference was observed in only two sera (strong positive to doubtful), and in both of these the intervening zone was just straddled These results support the conclusions already reached, and are comparable with the reproducibility obtained with repeat tests on the same specimens of serum with the STS

The results of tests on more than one serum from the same patient are shown in Table III Where there were more than two specimens and the results were discrepant, the strongest and weakest results are shown These, in all cases, were the first and last serum examined

TABLE III
RESULTS OF REPEAT SERA ON 283 PATIENTS

Last Specimen	First Specimen		
	Positive	Doubtful	Negative
Positive	165	2	0
Doubtful	4	10	3
Negative	Early syphilis treated 3 Normal infants 2 Tabes treated 1 } 6	Early syphilis treated 4 Latent syphilis treated 1 I K 2 ?Congenital syphilis treated 1 } 8	85

Among the 283 patients, 260 (92 per cent) showed complete agreement of results In five (1 8 per cent) there was an apparent increase in the strength of the reaction, but no cases changed from negative to positive In seventeen patients (6 per cent) there was an apparent decrease in strength, and six of these (2 1 per cent) changed from positive to negative These six cases comprised one of treated primary syphilis, two of treated secondary syphilis, and one of treated latent syphilis In addition, there were two clinically normal infants whose TPI tests were found to be positive after birth, and whose mothers had been treated for latent syphilis during pregnancy These two cases probably represent a passive transfer of maternal antibody and its gradual disappearance While immobilizing antibody disappears more slowly than reagin, it does not persist longer than some other antibodies Serological results of four of these six cases on whom more than two TPI tests were carried out are shown in Figs 6 to 9 The long period between treatment and the change in the TPI test from positive to negative in Fig 9 suggests that the TPI may show a reduction in titre for a very long period after treatment In none of the six cases was the change from positive to negative at variance with the clinical findings

Conclusion

The reproducibility of the TPI, as assessed by the analysis of results obtained with negative sera and

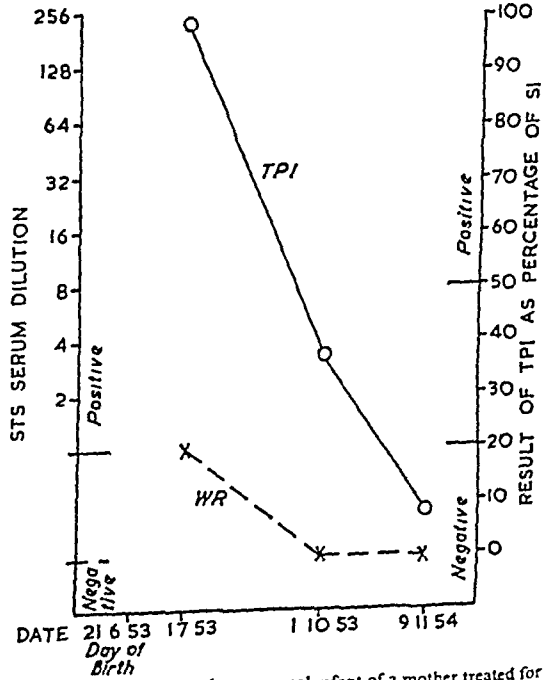

FIG 6.—TPI and STS results in normal infant of a mother treated for latent syphilis showing spontaneous disappearance of antibodies

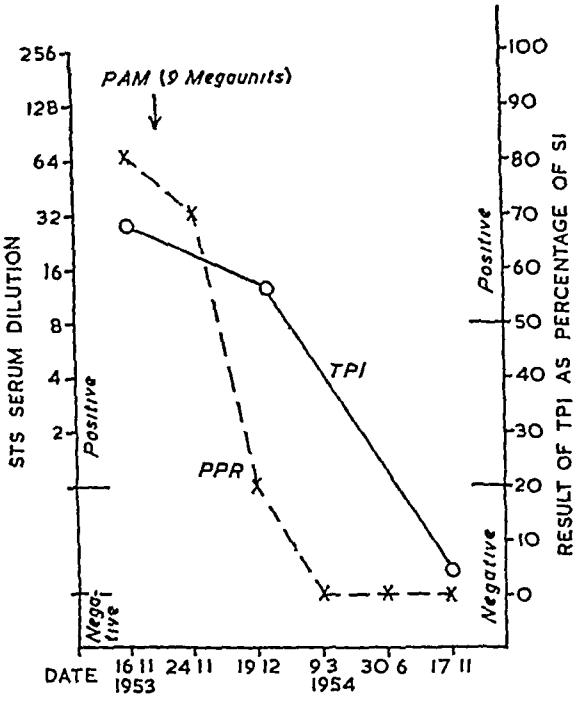

FIG 7.—TPI and STS results in male aged 22 yrs with 2 weeks history of a genital sore of treated primary syphilis showing disappearance of antibody following treatment with penicillin

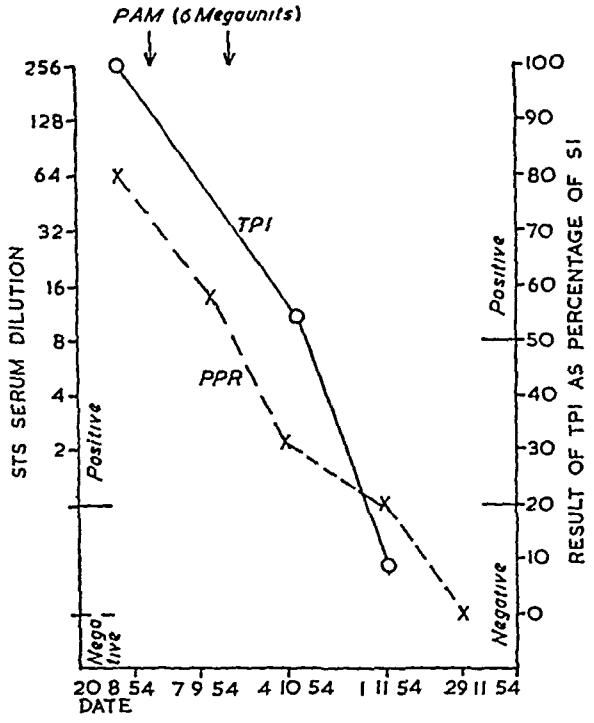

FIG 8.—TPI and STS results in female aged 26 yrs with 2 weeks history of rash of secondary syphilis showing disappearance of immobilizing antibody after treatment with penicillin

positive control serum, is comparable to that of the STS This conclusion is supported by the results of repeated tests on the same sera and tests on different sera from the same patients

SPECIFICITY

In the immediate post-war years, the problem of suspected non-treponemal reactions with the STS was acute, especially in the U S A The application of the TPI to this problem, without prolonged assessment of the test, would appear to be justified in that no reported cases with non-treponemal reaction based on confirmed TPI results have developed other evidence of syphilis

The acceptance of the test as a highly specific one for the treponematoses would, however, appear to be based upon the use of virulent treponemes as the antigen rather than upon experimental evidence Zellmann (1954) was

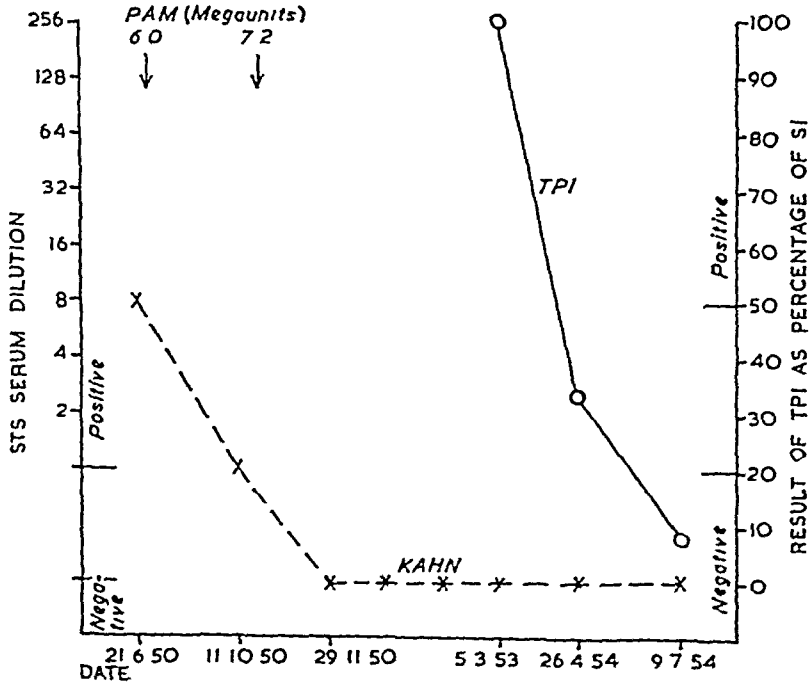

FIG 9.—TPI and STS results in a case of secondary syphilis showing disappearance of immobilizing antibody 5 yrs after treatment Female aged 38 yrs with history of 3 months rash and 2 months hoarseness

able to collect reports from the literature on only 1,249 non-syphilitic patients to which he added a further 148 cases of his own (total 1,397) Of this total, 289 cases included in the non-syphilitic group would appear to be the same cases as those grouped by Chacko (1953) into 109 normal individuals, 132 cases with diseases other than syphilis, and 48 cases suspected on clinical grounds of giving non-syphilitic reactions with the STS Excluding these, the total number then reported by Zellmann was 1,108, of which the largest series was 241 patients reported by Chacko

The TPI would appear to be specific in the immunological sense, that is, based upon a true antigen-antibody reaction, as it consists of an extremely elegant interaction between organism, antibody, and complement Its specificity in practice will therefore depend on the uniqueness of the antigen and therefore upon the antibody involved The sharing of antigens by related species is the rule rather than the exception Well known examples are the treponematoses, the Salmonella, and the viruses of the Lymphogranuloma-Ornithosis group The sharing of antigens by unrelated species, while not common, is illustrated by the agglutination of strains of *Proteus* by serum from cases of Rickettsial infection (Weil-Felix reaction) and the occurrence of serologically similar capsular antigens in the Type B Friedlander Bacillus and the Type II Pneumococcus In each of these examples, the shared antigen is a polysaccharide, and, in addition, each organism contains a specific antigen with which no cross-reaction occurs Hardy and Nell (1955) have shown that the *Treponema pallidum* can be agglutinated by two antibodies, one of which can be absorbed with lipid antigens and is presumably Wassermann reagin, the other being a specific anti-treponemal antibody which may be identical to immobilizing antibody It seems, therefore, that *Treponema pallidum* contains not only a lipid antigen related to substances occurring widely in nature which forms the basis of the STS, but also one or more specific antigens The sharing of two dissimilar antigens with unrelated species would appear extremely unlikely

If the antibody that immobilizes the *Treponema pallidum* in the presence of complement occurs in conditions other than treponemal infections, the antigen that stimulates its production must have a relationship with some factor or disease with which its association might be demonstrated, as has been done with some of the causes of non-treponemal reactions with the STS The number of non-syphilitic cases so far studied with the TPI is as yet insufficient to demonstrate any such association

If immobilizing antibody only occurs in treponemal infections, the natural history of these diseases and the extreme persistence of immobilizing antibody make it virtually certain that a proportion of cases with positive TPIs will have no other evidence of treponemal infection It therefore follows that the absolute estimation of the specificity of the TPI will not be possible for a considerable time

RESULTS AND DISCUSSION

The sera reported here are divided into three groups

(*a*) 323 patients attending the antenatal clinics of the Royal Free Hospital These were selected on the basis of having negative STS

(*b*) 103 individuals classified as non-syphilitic, comprising 92 patients attending the Royal Free Hospital with diseases other than syphilis, and eleven normal individuals

(*c*) 345 patients attending the Whitechapel Clinic, London Hospital, who were presumed to be non syphilitic (These cases have already been reported by Wilkinson, 1954)

The results of the TPI in these cases are shown in Table IV, together with the totals collected by Zellmann (1954)

TABLE IV
TOTALS OF PRESUMED NON SYPHILITIC CASES

Reference and Category	Totals	Result of TPI		
		Positive	Doubtful	Negative
After Zellman (1954)				
Normal	389	0	0	389
Diseases other than syphilis	615	1	1	613
Non syphilitic	393	2	0	391
Total	1,397	3	1	1 393
Less non syphilitics of Chacko (1953)	289	2	0	287
CORRECTED TOTALS	1 108	1	1	1 106
Wilkinson (1954)				
Clinic cases presumed non syphilitic	345	10	2	333
Sequeira				
Unselected antenatal patients with negative STS	323	3	0	320
Non syphilitic	103	0	0	103
Totals	771	13	2	756
Less possible syphilis and defaulters	11	10	1	0
CORRECTED TOTALS	760	3	1	756
GRAND TOTALS	1 868	4	2	1 862

Brief clinical details of all positive and doubtful cases are shown in Table V Among 1,879 patients initially presumed to be non-syphilitic, seventeen gave positive or doubtful TPI results Of these

TABLE V

CASES INITIALLY DIAGNOSED AS NON SYPHILITIC IN WHOM THE TPI WAS FOUND TO BE POSITIVE OR DOUBTFUL

Reference and Category	TPI Result	(% SI)	Notes
Zellman (1954) 103 cases with diseases other than syphilis	Positive	—	Paroxysmal auricular fib rillation no history or signs of syphilis
	Doubtful	—	Disseminated sclerosis no signs or history of syphilis
Wilkinson (1954) 347 V D clinic cases classed as non syphi litic	Positive	(94)	British West Indian Emi grated not available for investigation
	Positive	(64)	British West Indian Vague history of yaws in childhood
	Positive	(60 60)*	Pakistani Treated for penile sore with injec tions at sea in 1954
	Positive	(100)	British West Indian Cut on penis in 1940 Treated with tablets and injection in Jamaica
	Doubtful	(45)	British West Indian At tended with gonorrhoea Defaulted
	Positive	(100)	British Guianan Cardio lipin W R positive on same specimen of serum
	Positive	(64)	History of I V injections in V D clinic 20 yrs ago
	Positive	(100)	Cardiolipin W R positive on same specimen of serum
	Positive	(91)	Husband with syphilitic glossitis Referred as contact of late syphilis
	Positive	(100)	Prostitute Defaulted
	Doubtful	(28)	Venereophobia Single specimen gave SIs of 48 19 33 12 per cent
	Positive	(78, 76)*	Venereophobia Vague his tory of injections for boils some years previ ously
Present Series 323 antenatal cases with negative STS	Positive	(100 96)*	History of twins dying soon after birth One child (hydrocephalic) TPI and STS negative
	Positive	(100)	Austrian History of I V injections in prison camp during war
	Positive	(100)	Parents and sibling said to be normal Central incisors missing were bad and crooked

* Two specimens examined

three were not available for further investigation, while in eight evidence was later found suggesting the possibility of previous treponemal infection Therefore, among the 1,868 patients finally presumed to be non-syphilitic, four (0 21 per cent) gave positive and two (0 11 per cent) gave doubtful reactions In none of these cases can syphilis be absolutely excluded as in no case was a full epidemiological study carried out It therefore appears that the occurrence of non-specific reactions with the TPI is not yet conclusively proved

To assess the possible significance of these TPI positive–STS negative results, it is necessary to consider the behaviour of the TPI in known cases of syphilis, and to examine the incidence of this pattern of results In early untreated syphilis, the STS become positive before the TPI, practically all cases of untreated secondary syphilis having a positive TPI (Magnuson and Thompson, 1949) In treated early syphilis, the TPI remains positive longer than the STS The behaviour of the TPI in latent syphilis is discussed elsewhere (Wilkinson and Sequeira, 1955) In late syphilis, the great majority of patients have a positive TPI which appears unaffected by treatment The few cases with a negative TPI are examples of very long standing congenital or acquired infection

There are, in addition, certain other sequels that are theoretically possible after infection with the *Treponema pallidum* The organism might be eliminated, either spontaneously or following the administration of antibiotics for some other condition, without any sign or symptom of syphilis being produced, or the normal manifestations of the disease might be suppressed without the eradication of the infection In either of these eventualities, production of immobilizing antibody might occur without the production of reagin That the latter phenomenon can occur in experimental syphilis has been demonstrated by Nelson (1952) In this experiment, he under-treated a group of syphilitic rabbits with penicillin, some of which reacted in the same way as the fully-treated controls In two, however, the reagin titre fell to negative, while the TPI titre fell and then rose At the end of the experiment, virulent *Treponemata pallida* were recovered from the lymph glands of these rabbits in spite of the negative STS The possibility of such cases occurring in man was examined as follows The TPI was carried out on the sera of patients with gonorrhoea at periods varying from 6 months to a year after treatment with penicillin Among sixteen such patients, in whom there was no history or clinical evidence of syphilis, one had positive STS and TPI, and one had negative STS and positive TPI This latter patient was an Englishwoman of 28 years whose gonorrhoea was treated with penicillin and who returned 2 months later with a gonorrhoea re-infection which was again treated with penicillin Her husband had neither signs nor evidence of syphilis or gonorrhoea Her TPI was found to be positive 10 months after her first attack of gonorrhoea, and was confirmed with a second specimen Her STS were negative throughout These results are inconclusive in that a TPI was not carried out on her first attendance

That negative STS and positive TPI cases analogous to untreated latent syphilis can occur, is suggested by the finding of five patients with this

prone than the other types to be associated with positive STS results has been widely mentioned in published reports Similarly, the failure to correlate bacteriological status or length of treatment of leprosy with the occurrence of BFP reactions has been previously reported by Badger (1931) and by Portnoy and others (1952) respectively

While there seems little doubt that leprosy is a cause of BFP reactions in individual cases, its effect in the aggregate is probably small The incidence of leprosy in the Eastern Province is estimated as 12 6 per thousand (Health Department Annual Report for 1950, Northern Rhodesia, 1951) From the series reported above it may be assumed that 18 4 per cent of lepers will give a false positive result to STS It follows that the incidence of BFP reactions due to leprosy will be approximately 0 24 per cent of the total population in this area

Summary

The literature on false positive reactions to the standard serological tests for syphilis is reviewed, with special reference to their occurrence in the tropics, and their association with leprosy and malaria Of the various laboratory procedures for the differentiation of true and false positive results, only the treponemal immobilization test is of proven value, and this is not, as yet, a practical proposition in most parts of Africa

In an attempt to assess the incidence of these false positive reactions, the Kahn results obtained from 6,797 successive adult African patients attending at V D clinics in the Eastern Province of Northern Rhodesia have been studied In 791, recorded details were insufficient to make a final assessment Of the remaining 6,006 patients, there were 1,889 in whom the Kahn test was persistently positive without overt signs of active syphilis

These 1,889 patients were further assessed in an attempt to decide whether their Kahn results were true or false positive reactions The factors considered in making the assessment are fully described together with their limitations It is realized that the figures given for the final assessment are only approximate It is estimated that, of the 1,889 potential latent syphilitics, somewhere between 9 and 17 5 per cent gave false positive results This gives an estimated incidence for the whole group (6,006) of somewhere between 2 8 and 5 5 per cent

Kahn tests were performed on 137 African patients with malarial parasites in the blood and 38 (27 7 per cent) were found to give positive or weak positive results The incidence of positive Kahn results among the children with malaria was higher than among the adults The theory is advanced that, in areas of endemic malaria repeated attacks of malaria starting in infancy may have a diminishing effect in producing false positive results, so that by the time adult life is reached malaria will play only a small part in producing false positives A suggestive degree of parallelism was observed between the monthly incidence of false positive results and that of malaria throughout the year

A total of 477 lepers were submitted to the Kahn test, and 18 4 per cent were found to give positive or weak positive results Positive results were twice as common in female as in male lepers A higher percentage of positive results was found among patients with lepromatous than with other types of leprosy The activity of the disease appeared to be an important factor in the occurrence of positive results While it seems certain that leprosy is a cause of false positive results in individual cases, the known incidence of leprosy in the population at large in this area and the relatively small number of lepers showing positive Kahn results at any one time suggest that, in the aggregate, the effect of leprosy will be small

Conclusion

It seems certain that in the majority of cases recorded here, the positive serological response could be equated with a syphilitic infection No claim is made that what is found in one tropical area will of necessity apply in all others, and the position will have to be ascertained in each new area The majority of false positive reactions are probably not due to one single factor but to a multiplicity of different factors

A plea is made that the finding of a positive serological test for syphilis in patients in the tropics should be followed by the same careful search for evidence of syphilis, or other treponematoses as is normally given to patients with a similar finding in temperate climates The practice of automatically disregarding serological positive results in Africans with no active manifestations of syphilis, simply because false positive results are commoner in the tropics, is deprecated To quote Stokes and James (1949)

> There can be no excuse for discarding or minimizing the serological test for syphilis because there are biologic or non-specific positive tests

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SKIN TESTING IN 246 PATIENTS WITH NON-SPECIFIC URETHRITIS WITH A REVIEW OF THE IMPORTANT LITERATURE *

BY

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The problem of non-specific urethritis (NSU) is receiving increasing attention, although its existence has been known for over 70 years (Bockhart, 1886), and the recognition of different types of urethritis preceded the discovery of the gonococcus (Neisser, 1879) by an even longer period (Schwediauer, 1784, Hernandez, 1812, Stevenson, 1823, Parker, 1839)

Waelsch (1901) described a special follicular NSU, which still goes by his name, it is subacute or chronic Hecht (1927) gave a good account of acute NSU The only common factor in all these cases appeared to be the absence of the gonococcus

The clinical problem of NSU came to the fore with the satisfactory diagnosis and rapid cure of gonorrhoea Up to the present, its infective nature is only apparent on epidemiological investigation, which depends largely on medical history of a particularly unreliable kind as it involves disclosure of venereal exposures Bound up with this difficulty is the fact that the limits of the incubation period are not known and a baffling though admittedly small number of patients, who deny firmly any preceding sexual intercourse, can be found in most large series The few limited epidemiological studies available seem to favour the spread of NSU by sexually active men and women (Durel and Siboulet, 1954) It may be, however, that immunological and microbiological research is more likely to help solve the aetiological problem Up to date, the main lines of investigations have been concentrated on five possible causes

(1) bacteria,
(2) virus,
(3) PPLO and L ' forms of bacteria,
(4) trichomonads,
(5) primary prostatic disorder

(1) *Bacterial Aetiology*.—Most bacteria normally found in the lower urogenital tract have been implicated but it is now generally agreed that only a small proportion of NSU cases is due to pathogenic strains of bacteria These could usually be grown in pure culture and they have responded to specific treatment The commonest organisms are coagulase positive *Staphylococcus albus* and *aureus, Streptococcus faecalis*, haemolytic streptococci, and diphtheroids Somewhat surprisingly *E coli* has only rarely been incriminated (Hughes and Carpenter 1948, Cohn, 1905, Harkness and King 1938)

More recently, Ambrose and Taylor (1953) reported the presence of small coccobacilli in NSU Its growth on culture media was strikingly slow and it may be due to this that the organism was overlooked in routine cultures Leopold (1953) found microbes related to the genus *Haemophilus*, which he thought to be of aetiological significance

(2) *Virus*.—Urethritis occurs at times with certain known virus diseases such as measles (Kidd 1917) herpes simplex (Nicolas Gate and Papacostas 1923) herpes zoster (Dubois, 1926) dengue fever (Weyrauch and Gass, 1946) mumps (Spence 1931), lymphogranuloma venereum (Hellerstrom 1929) and inclusion blennorrhoea (Harrison and Worms 1939) Of this heterogeneous group the last named is of the greatest interest, largely due to the work of two ophthalmologists, Lindner and Thygeson, who established a close connexion between inclusion conjunctivitis of infants and adults on the one hand and certain genital infections on the other

Lindner (1909 1911 1913) demonstrated epithelial inclusions in the genital tracts of mothers whose infants suffered from inclusion conjunctivitis He then produced experimentally inclusion conjunctivitis in monkeys by inoculating them with vaginal secretions of these women It was his belief that the infective agent was identical with or possibly an attenuated trachoma virus

The other ophthalmologist Thygeson (1934) showed that the virus of inclusion conjunctivitis now called *Chlamydozoon oculo-genitale* belongs to the psittacosis ornithosis lymphogranuloma group and is distinct from trachoma virus In animal experiments and epidemiological studies he produced some evidence that inclusion conjunctivitis of infants and also of adults could be caused from minimal genital infections and that the virus was capable of surviving in water for several hours This led to the idea that the virus may spread from the

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genito-urinary tract to the eyes in non-chlorinated swimming pools, using the water as its vehicle No evidence has been adduced for infectious spread to the genital tract in swimming pools Experimentally he was able to produce ' inclusion cervicitis " in baboons by inoculations, but failed to provoke inclusion urethritis in either male or female baboons Thygeson concludes that *C oculogenitale* causes a benign, chronic, but self-limited urethritis in the male, and an almost symptomless inflammation of the external cervical os in the female Transmission is by sexual intercourse Unhappily the virus has not yet been cultivated and apart from the animal transmission referred to, the stained inclusion bodies in epithelial scrapings are the only means of identification (Thygeson , 1934, 1954) Clinically he describes ' inclusion urethritis " as a self-limiting minimal urethritis, as a rule without complications, its minimum duration being 5 months, the maximum 11 months (Thygeson, 1954)

It should be mentioned here that we found such a clinical picture amongst our cases, but only in a small number

(3) *Pleuropneumonia-like Organisms (PPLO)* —Although these infectious agents were cultivated in 1898 by Nocard and Roux from contagious bovine pleuropneumonia, it was only since Dienes found similar organisms in an otherwise ' sterile " Bartholin s abscess (Dienes and Edsall, 1937) that the possibility of its pathogenicity in humans was seriously considered Dienes and his co-workers were able to show that PPLO were frequent inhabitants of both the male and female genito-urinary tract At first, as is so often the case, the organisms were reported to occur only in the presence of some infection, notably ' Non-gonococcal urethritis " (Beveridge, Campbell, and Lind 1946 Harkness and Henderson-Begg, 1948) Recently, however, PPLO have been found in apparently normal male urethras and even more frequently in the normal female urogenital tract (Salaman and others, 1946 , Harkness, 1950 , Randall, Stein, and Ayres, 1950 , Melen and Linnros, 1952 , Nicol and Edward 1953) The question of pathogenic and non-pathogenic strains is receiving special attention at present and their position in ' non-specific " genital infections is uncertain Perhaps the most important observation to date is the isolation of pure cultures of PPLO in otherwise sterile " inflammatory lesions, such as salpingitis, bartholinitis, and from the synovial fluid of Reiter s arthritis (Dienes, Ropes, Smith, Madoff, and Bauer, 1948 , Warthin, 1948) It was apparently the sole organism in some cases of cystitis and pyelitis in men (Dienes and Berg, 1954) An interesting suggestion came from Klieneberger-Nobel (1954) when she described animal experiments with originally non-pathogenic PPLO which became virulent if certain other organisms were also introduced This activating action deserves further study in man Willcox (1954b) reported therapeutic success with erythromycin in NSU, and, as PPLO is highly resistant to this antibiotic, its aetiological significance is questioned (*Lancet*, 1954) Ruiter and Wentholt (1952) instilled PPLO cultures intra-urethrally into two volunteers without any subsequent clinical or bacteriological evidence of infection They also noted that abundant growth of PPLO was found only in men with genital infections and, when controls did show the organisms, growth was scanty In conclusion it may be said that the position of PPLO in human genital infections is unsettled

When Klieneberger-Nobel isolated a PPLO from a culture of *Streptobacillus moniliformis* in 1935, a different line of investigation was initiated She called these micro-organisms " L organisms ", and it is now generally thought that the L-phase is a variant of the bacterium or part of its life-cycle Its cultural and other characteristics resemble the true PPLO closely, but it is considered that the risk of confusion is not great (Sorel, 1954 , Edward, 1954) A number of bacteria have now been found capable of producing L-forms, but they still retain some of the characteristics of the parent bacterium, *e g* , the L-forms of *Proteus vulgaris* possess the characteristic smell (Edward, 1954) and generally the L-phase is difficult to subculture and readily reverts to the bacillary form it stems from PPLO, on the other hand, are apparently stable The possibility of gonococci giving rise to L-forms and thus being responsible for NSU was considered by Salaman and others in 1946 when they demonstrated these forms in gonococcal cultures This suggestion, however, has not found general acceptance, and Salaman himself considered alternative explanations such as double infections

(4) *Trichomonas Vaginalis* —This protozoon was first noted in male urethral discharge by Kunstler in 1883 and since that time the percentages of positive findings have varied greatly with different authors (Freed, 1945, 1948) The recent introduction of routine cultural methods in some centres resulted in somewhat higher positive returns , Sorel (1954) observed 11 2 per cent in 527 patients, but only one of them was acute, the rest with trichomonas having chronic urethritis

He also found the parasite in the apparently healthy urethras of men whose wives suffered from trichomonas vaginitis Thus, as with all other alleged causes of non-gonococcal urethritis, the microbial agent has been demonstrated in the apparently healthy urethra

Lanceley and McEntegart (1953) inoculated cultures of trichomonads intra-urethrally into five male volunteers, all of whom developed urethritis, yet trichomonas could only be recovered in three of them In conclusion, it is not thought likely on present evidence that trichomonas is a major cause of male urethritis

Mycotic Infection —Fungal elements have from time to time been reported in urethral discharges as isolated findings, but recently Auckland and Preston (1954) found them present in 36 out of 722 males with urethral discharge The possibility of the world-wide use of antibiotics in the last decade, resulting in an increased pathogenicity of fungi, may account for the relatively high proportion found in this series, but there is *no* proof that the fungi are anything but saprophytic, and in any case they have not been found in important numbers in any other series

The extent of the problem of NSU in England and Wales may be judged from the Ministry of

Health returns (1954) which have listed NSU as a separate condition since 1951 The number of NSU cases attending the V D clinics of England and Wales in 1951 was 10,794 as against 14,975 male gonorrhoea cases, in 1952, 11,552 NSU cases as against 15,510 male gonorrhoea, and in 1953, 13,095 cases of NSU as against 15,258 of male gonorrhoea

The two sets of figures are in our opinion not strictly comparable for these reasons

(1) Whereas gonorrhoea is promptly cured by penicillin, leaving a negligible number of relapses, the position is different with NSU, here treatment is less specific and relapses are common If they happen to follow fresh sexual exposure (and there is some evidence to suggest that even non-infectious intercourse may reactivate latent infection), they are likely to be counted as a new attack of NSU

(2) The diagnosis of gonorrhoea in the male is straightforward, but that of NSU depends on negative properties and is thus less easily definable

In addition, NSU has a wider range of severity than gonorrhoea, with a special tendency to minimal and intermittent signs Some of these may in fact not be NSU, but may be due to increased secretions of an otherwise normal genital tract This is commonly associated with venereophobia The distinction, however, is not always clear and diagnosis will vary with the inclination of the physician concerned Interesting numerical expression of the problem can be found in the classification of a large series of "urethritis" (Durel and Siboulet, 1954) of 2,000 patients attending male urethritis clinics

Disease	No of Cases (per cent)
Gonorrhoea	40
NSU	23 6
Unimportant discharges and gonophobia	30 6

Thus the "unimportant discharges constitute a sizable group, and it is plausible that, until we have a certain way of diagnosing NSU its incidence cannot be accurately determined

With the strongly held rival views on the causation of NSU it is not surprising that at the Symposium on Non Gonococcal Urethritis held at Monaco (1954) the question of aetiology was kept open without any line of investigation having been found more promising than any other In fact some inclined to the view that the causes may be many even though clinical differentiation is as yet not possible

The recent series of patients who have been investigated in order to find the major aetiological factor, mainly by workers in the United States France, and Great Britain are set out in Table I (opposite)

The present position with respect to NSU may be summarized as follows

(i) Infection is the probable cause but has not been proved for the majority of cases,

(ii) Epidemiological studies have not been used on a scale large enough to extract all the information they are capable of giving,

(iii) Experimental NSU has not yet been produced in men with any of the suggested infective agents except for the small series with *Trichomonas vaginalis*,

(iv) *C oculogenitale* has defied culture so far

(v) The position of PPLO and L forms is uncertain in the aetiology of any human infection, the question of pathogenic strains and of activating factors being involved in changing harmless strains into virulent ones are problems receiving increasing attention and the fact that PPLO are present in many of these cases in abundant culture has been stressed (Rutter and Wentholt, 1953),

(vi) The thesis of a pre existing quiescent inflammation of the peri urethral glands leading to a descending urethritis has been again put forward as a major cause of NSU and needs careful consideration

(vii) The suggestion by Coutts (1937 1948) and Adis (1948) that a spirochaete may play a responsible role in the aetiology has not been favoured,

(viii) Reiter s syndrome has been considered by many to be very closely related to NSU the subject has been fully reviewed by Harkness (1950) and Duguet (1952)

Skin Tests

Skin tests have been used in this study to determine whether an altered skin sensitivity existed in NSU, and, if so, to discover whether this skin response was of a specific nature

The mechanisms of immunity and hypersensitivity whereby the body responds to the challenge of infecting agents, have been studied and made use of in medicine for a long time

In the field of venereal infection one is reminded of the pioneering work with skin tests of Frei (1925) in lympho granuloma venereum Noguchi (1911) and Kolmer and Greenbaum (1922) in syphilis Engel and Grundmann (1933) in gonorrhoea Ito (1913) and Reenstierna (1924) in chancroid, Kornblith (1944) in granuloma inguinale and Adler and Sadowsky (1947) in *Trichomonas vaginalis*

The many factors which affect the results in skin testing in infectious disease have been summarized by Beerman and Ingraham (1950) On the technical side certain factors make standardization of the skin test very difficult e g the non specific response of the skin to animal tissue as with mouse brain tissue in the Frei test the concentration of antigen dosage times of reading the tests definition of test results

TABLE I

RECENT MAJOR WORK ON THE AETIOLOGY OF NSU

Aetiological Agent under Investigation	Authors	Year	No of Patients	Results
1 Bacteria *	Hughes and Carpenter	1948	117	All thought to be ' bacterial
	Harkness	1950	144	25 5 per cent thought to be bacterial '
	Willcox	1954a	81 NSU 105 Controls	No significant difference bacteriologically between the two groups
2 *Trichomonas Vaginalis*	Freed	1948	112	28 5 per cent positive
	Sorel	1954	527	11 2 per cent positive
	Lanceley and McEntegart	1953	310	5 3 per cent positive
	Durel and Siboulet	1954	412	10 2 per cent positive
3 Pleuropneumonia like Organisms (PPLO)	Harkness and Henderson Begg	1948	839 NSU 139 Gonorrhoea 50 Male controls	16 per cent positive 9 per cent positive 0 per cent positive
	Melen and Oberlad	1952	61 NSU 60 Controls	18 1 per cent positive 16 6 per cent positive
	Durel and Siboulet	1954	631 NSU	7 4 per cent positive (same proportion of PPLO in urethritis of all degrees)
	Nicol and Edward	1953	140 NSU 110 Male controls 35 Cervicitis 40 Female controls	25 7 per cent positive 12 7 per cent positive 48 5 per cent positive 22 5 per cent positive
	Shepard	1954	42 NSU	71 per cent positive
	Brisou	1954	350 NSU	12 7 per cent positive
	Dienes and Berg	1954	86 NSU 67 Controls	64 per cent positive 27 per cent positive
	Randall and others	1950	300 Cervical cultures	26 per cent positive
4 Inclusion Urethritis	Bedson	1950	25 NSU	None positive
	Thygeson and Stone	1942	100 NSU and Gonorrhoea	8 per cent positive
	Durel and Siboulet	1954	2 328 NSU	3 5 per cent positive
	Willcox	1954a	250 NSU 108 Gonorrhoea	27 6 per cent positive 21 7 per cent positive
5 Fungi	Auckland and Preston	1954	602 NSU 120 Gonorrhoea	5 per cent positive 5 per cent positive
6 Primary Prostatic Diseases	Ambrose and Taylor	1953	Considered that 25 to 30 per cent of young males have primary silent chronic prostatic infection causing secondary urethritis	
	Graham	1954	Believed that a prostatic dysfunction is present in a large proportion of patients who show recurrent infection of the urethra	

* The coccobacillus (Ambrose and Taylor 1953) and haemophilus (Leopold 1953) isolated in cases of NSU are too recent and unconfirmed to be included

According to Beerman and Ingraham, three types of skin test reaction may occur a rapid histamine-like reaction, delayed or tuberculin-like reaction, or a late eczematous reaction The second type, due to tissue allergy, is the commonest

Skin tests have been used before in the study of NSU and Reiter s syndrome, but their use has been limited to a few cases Harrison and Worms (1939), in their review of the problem of inclusion urethritis, remind us that Frei, Wiese, and Klestadt (1932), Kalz (1933), and Bezecny (1934) all showed that an allergic reaction could be obtained in lymphogranuloma patients using urethral discharge from a case of Waelsch urethritis Conversely, allergic skin reactions in a patient with Waelsch urethritis could be obtained using Frei antigen (Bezecny 1934, Fahlbusch and Zierl, 1937 Bizzozero and Midana, 1938 , and Ross, 1939)

More recently Storm-Mathisen (1946), Thiers and Joly (1948), Harkness and Henderson-Begg (1948), and Thygeson (1954) have reported similar work Storm-Mathisen used gland emulsion and joint exudate as the antigen for skin testing, Thiers and Joly used urethral pus, Thygeson urethral scrapings, and Harkness and Henderson-Begg phenolized suspensions of "L" organisms Very few cases were investigated in this way, and only Thygeson reported completely negative results

Method

In this study the antigen for skin testing was prepared from the urethral secretions of patients with non-bacterial urethritis The platinum loop scraping was mixed with normal saline This mixture was first subjected to high speed centrifugation for 15 min , and the supernatant fluid was then withdrawn and incubated at 60° C for 1 hr Before use the fluid was tested for bacteriological sterility, and 0 5 per cent phenol was added

For the skin test, 0 2 ml was injected intradermally in the forearm, and the result was read after 48 hrs The test was considered positive when there was a papule with erythema of 1 cm or more in diameter Each fresh batch of skin test material was, of course, of unknown antigenic potency and had to be tested against an already proved sensitive patient for its capabilities to be known It was this problem which made the process difficult and used valuable quantities of meagre skin test material For this reason, many of the lots were pooled before use

The donor material was made up at two centres and exchanged by the authors, until it was clear that similar results were being obtained with each group of materials

Control over the donor skin test material was maintained by

(*i*) using a control injection of sterile 0 5 per cent phenol in normal saline ,

(*ii*) preparing antigen in a similar fashion from cases of acute gonorrhoea ,

(*iii*) skin testing a group of patients who did not have NSU

This control group was largely made up of cases of acute gonorrhoea, since it was considered very desirable to try to eliminate the possibility of a non-specific response to urethral tissue

Results and Discussion

In the assessment of this experiment 246 cases were used The ages of the three groups of patients, NSU, gonorrhoea, and non-venereal demonstrated the slight bias, noted by others, in NSU towards the less young patient as compared with acute gonorrhoea

In the case of the married patient, positive skin reactions occurred with equal frequency in those who had, as those who had not, a history of extramarital exposure The disease did not favour either the single or the married man , there were 105 single and 58 married with NSU in the study

It has often been said that these patients include a high proportion of men who indulge in excessive numbers of risks, or in excessive intercourse with the female This was not the finding of this study

The incubation periods disclosed a wide variation, but many of the apparently shorter incubation periods may well have been longer owing to failure of the patient to declare every risk

It is noteworthy that many authorities consider that the longer incubation period belongs to the commoner type of NSU The accompanying figures demonstrate the inconclusiveness of this factor

Incubation period (weeks)	1	2	3	4
No of patients	21	19	21	34
Skin tests positive (per cent)	67	70	70	73

A positive skin reaction was obtained quite early in the patient's disorder, the majority being tested within the first few days of attendance

Positive reactions unexpectedly tended to occur more frequently in those patients who responded more rapidly to treatment The skin test results were tabulated against the response to treatment in 162 patients, 107 of whom responded well and 55 badly The standard therapy for purposes of the study, which is not considered more than 55 per cent efficient by Harkness, was streptomycin in conjunction with sulphonamides Positive reactions were noted in 46 per cent of the patients who responded well, and in 36 4 per cent of those who responded badly to therapy, and were negative in 21 per cent and in 33 per cent respectively These figures, although not really significant, are suggestive

Similarly, 94 results were arranged so that the response to treatment was set against incubation periods (considered as either of the shorter or longer type) , 23 cases had an incubation period of 10 days or less, and 71 of over 10 days Seventy-nine per cent of those with the shorter incubation period responded to treatment rapidly, 60 per cent giving a positive, and 30 per cent a negative skin reaction Of those with the longer incubation period, approximately equal numbers responded rapidly and failed to respond to therapy, 55 per cent giving fully positive and 15 per cent negative results

Of seven cases whose donor skin test material was used unpooled and alone, in whom a complete record of their results was available, the incubation periods lay between 14 and 26 days , they all responded positively to the skin test, and their treatment responses (rapid or poor) were equally divided

Fairly extensive multiple testing of the individual patient was undertaken in order to test the patient s ability to retain the allergy Some cases who

started negative, did not show a positive response until the second or third week The skin response remained positive in some cases for many weeks and seemed to become negative within 2 months There were many exceptions, and the numbers were too small to draw hard conclusions The cases who were negative at the end of the second week more often than not remained so

Table II shows the results of the experiment as a whole In 137 cases of NSU, 53 3 per cent gave fully positive results, and 30 per cent negative If the weakly positive results are added in turn to the positive and negative groups it appears that at best 70 per cent and at worst 47 5 per cent gave positive skin test reactions The insertion of the doubtful NSU group gives some idea of the usefulness of this type of test in an incompletely diagnosed case

TABLE II
DETAILS OF THE SKIN TEST RESULTS IN 246 CASES

Disorders	Number of Patients		
	Positive	Weak Positive	Negative
NSU	72	24	41
Probable NSU	11	3	11
Gonorrhoea	1	3	30
Gonorrhoea + NSU (double infection)	3	1	2
Reiter s syndrome	3	1	4
Others *	1	0	35

* Healthy patients venereophobia syphilis lymphogranuloma venereum and general medical cases

Weight was added to the overall figure for skin reactions in NSU when it was apparent that the results from the three centres concerned in the work were very similar (Table III)

TABLE III
DETAILS OF SKIN TEST RESULTS IN NSU FROM THREE INDIVIDUAL CENTRES OF STUDY

Hospital	Number of Patients		
	Positive	Weak Positive	Negative
Seamen s	20	2	12
St Mary s	25	10	16
Guy s	27	12	13

The skin test was positive in several cases of acute gonorrhoea that did not respond to the specific therapy for that disease In typical cases of gonorrhoea there were negligible reactions

The fact that about half the small number of cases of Reiter's syndrome responded to the skin test was not unexpected Many workers have demonstrated a skin test response in these cases The fact that the arthritic syndrome rarely follows immediately upon the urethritis may have some significance

The heterogeneous group of control cases in Table II contained only one reactor

Antigen for skin testing, made up from cases of acute gonorrhoea, and tested in over two dozen patients, resulted in one positive and one weak positive reaction in gonorrhoea, and one positive and one weak positive in NSU

The local application of steroid hormone (hydrocortisone ointment, 1 and 2½ per cent) was undertaken in 39 cases of all types of NSU There was a striking symptomatic improvement in almost every case, and the meatal epithelium appeared less red and moist The urine however contained a first glass haze and debris, and a return of the urethral discharge was either immediate or delayed a week or so following cessation of therapy In a few cases inclusions were noted in the scrapings from the urethra after steroid therapy when they had not been noted before This requires further study

What was the nature of the allergen in the skin test? Since the controls gave practically no response, it is thought unlikely that a non-specific reaction underlies these results Two known allergens, lymphogranuloma venereum, and *Trichomonas vaginalis* in the female, produce positive skin test responses On present evidence, virus infection or an infection in which pleuropneumonia-like organisms have a role would seem the most likely explanation of the high proportion of skin test reactions

SUMMARY

The results of a skin testing experiment in 246 patients is described In 137 cases of NSU and seventy controls between 50 and 70 per cent of cases of NSU gave positive reactions, whereas a very small number of controls were positive to the test

It is suggested that between 50 and 70 per cent of cases of NSU are due to a predominating cause, and that an infecting agent in all probability exists in these cases

The skin test reactions were of the delayed or tuberculin type A few cases of the immediate type of reaction were noted but not included

The authors acknowledge with gratitude the generous assistance given to them by Dr G L M McElligott, Mr V E Lloyd, and Dr D Erskine in whose clinics the work was undertaken , and to Professors R Cruikshank and R Knox in whose departments the

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INCLUSION BODIES IN NON-GONOCOCCAL URETHRITIS ALSO SKIN LESIONS WITH INCLUSIONS *†

BY

A SIBOULET

Paris

In a recent statistical survey of 2,756 cases of non-gonococcal urethritis examined at the Urological Clinic of the Faculty of Medicine in Paris (Hôpital Cochin), inclusion bodies were found in 84, *i e*, an average of about 3 per cent In patients suffering from the urethro-conjunctivo-synovial syndrome, we have found, as previously reported by Harkness (1945), inclusion bodies in scrapings from the urethra and skin lesions We have always been particularly careful in the identification of inclusion bodies, and only record their presence when there are distinct nucleus and cell boundaries, elementary bodies stained a definite violet-purple with Giemsa, granules of regular size, clearly delimited crescent-shaped grouping, etc (Figs 1 and 2)

To confirm a viral aetiology, it is necessary, as Willcox, Howard, and Findlay (1954) remarked, to have the confirmation of serological tests (complement deviation of the psittacosis, ornithosis group), skin tests (obtained with lymphogranuloma venereum, psittacosis, trachoma antigen group), and cultures with transmission to animals in addition to finding inclusion bodies similar to those in the accepted virus diseases Observing these criteria, we have found in certain cases that the inclusion bodies present in epithelial cells from the urethra have all the characteristics of those described in other virus diseases

FIG 1 —Inclusion bodies

FIG 2 —[illegible]

* Received for publication May 5 1955

† One of a series of short papers read to the M S S V D on March 25 1955

TABLE

SITE THERAPY AND RESULTS OF TEN CASES OF URETHRITIS AND SKIN LESIONS WITH INCLUSIONS

Case No	Age (yrs)	Sex	Clinical Diagnosis	Site of Inclusion Bodies				Serological Tests				Treatment	Results
				Urethra	Conjunctiva	Synovial Membrane	Skin Lesion	Standard	Immobilization (per cent)	Cold Agglutination	Complement Deviation Reaction Psittacosis Group		
1	35	Male	Urethro conjunctivo synovial syndrome + ectodermosis erosiva pluriorificialis	+	+		+	Transitory +	0	−	−	Terramycin 18 g	Favourable Contact *treated*
2	33	Male	Urethro conjunctivo synovial syndrome + ectodermosis erosiva pluriorificialis	+	+	+	+	−	2	−	+	Aureomycin 20 g 2	Fair
3	35	Male	Urethro *conjunctivo* synovial syndrome + ectodermosis erosiva pluriorificialis	+			+	Transitory +	0	−	−	Terramycin 8 g	Good
4	29	Male	Urethro conjunctivo synovial syndrome + ectodermosis erosiva pluriorificialis	+	+	−	+	−	0	−	−	Aureomycin 12 g then Terramycin 20 g 2	*Cure* after systematic treatment of partners
5	44	Male	Urethro conjunctivo synovial syndrome + ectodermosis erosiva pluriorificialis	+	−	−	+	−	0	−	+	Terramycin 9 g 2	Good
6	36	Male	Urethro conjunctivo synovial syndrome + genital ulcerations	+	−		+	Transitory +	4	−	−	Terramycin 10 g Cortisone	Fair
7	38	Male	Urethro conjunctivo synovial syndrome + genital ulcerations	+	−	−	−	−	0	−	−	Aureomycin 10 g × 2	Favourable
8	29	Male	Urethro conjunctivo synovial syndrome − genital ulcerations	−	−	−	+	−	0		−	Terramycin 10 g Erythromycin Aureomycin 10 g	Fair
9	33	Male	Urethritis + buccal ulcerations	−			+	−	6	−	−	Aureomycin 10 g	Good
10	24	Male	Urethritis + buccal ulcerations	−	−		−	−	2	−	−	Terramycin 10 g 2	Good

The ten patients reported have all suffered from dermatological manifestations in addition to urethritis five cases of the urethro conjunctivo synovial syndrome with ectodermosis erosiva pluri

orificialis, three cases of the urethro-conjunctivo-synovial syndrome with genital ulcerations, and two cases of urethritis with buccal ulcerations (Table)

The microphotographs (Figs 1 and 2) and the summary of these ten cases show that the inclusion bodies detected are morphologically indistinguishable from those found in the recognized viral diseases Such inclusion bodies, however, were found in only about 3 per cent of the cases of non-gonococcal urethritis in our statistical survey

The pathogenicity of these inclusions is suggested by

(*a*) their disappearance when the treatment prescribed has proved clinically successful,

(*b*) their persistence after failure of treatment,

(*c*) their reappearance after renewed contact with one or more of the non-treated partners,

(*d*) their definite disappearance after effective antibiotic treatment of both patient and partners,

(*e*) failure to find this type of inclusion body in 150 persons with clinically healthy urethrae

Lastly, it is emphasized that, in the same patient, inclusion bodies of the same type were found in epithelial cells of the urethra, the conjunctiva, and skin lesions, especially in ectodermosis erosiva pluriorificialis

I should like to thank Dr A H Harkness for introducing me to this very interesting and absorbing subject, and Mesdames Jouveau-Dubreuil and Slomkowski for their technical help

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ELECTROCARDIOGRAPHIC CHANGES IN REITER'S SYNDROME*†

BY

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It is generally agreed that induced fever (intravenous vaccine, hyperthermy, inductothermy) provides one of the most effective methods of treatment of Reiter's syndrome (Harkness, 1950, Willcox, 1950), but, although the disease occurs most frequently in young males, the use of this potentially dangerous form of therapy must be conditional on the patient passing a thorough pre-fever investigation This normally includes complete clinical examination, chest radiography, electrocardiography, and an estimation of the blood urea nitrogen

During the past year, two young men with Reiter's syndrome have been found on routine examination to exhibit grossly abnormal electrocardiograms without any accompanying clinical evidence of cardiovascular disease It is impossible to be certain whether or not the relationship is more than adventitious, but, if it should emerge that Reiter's syndrome is capable of producing sub-clinical cardiac damage, this may of itself constitute a contraindication to one of the most effective forms of treatment yet known for the condition

Master and Jaffe (1934) noted abnormalities of the P-R interval and T waves in nineteen cases of gonococcal arthritis Gadrat and Morel (1935) found electrocardiographic changes in a man with gonococcal urethritis and arthritis, and Bang (1940) made an electrocardiographic diagnosis of gonococcal myocarditis in six men, five of whom had "recurrent specific arthritis", and the sixth acute urethritis and arthritis

Lever and Crawford (1944) described the case of a man, aged 37, already in hospital with the complete Reiter's syndrome who died 2 days after the onset of sub-sternal oppression cyanosis, and hypotension An electrocardiogram shortly before death was suggestive of recent anterior myocardial infarction, whereas one taken 6 days previously had been normal

Candel and Wheelock (1945), in a study of eleven patients with diverse conditions all showing electrocardiographic changes typical of myocarditis, encountered three cases of gonococcal arthritis and myocarditis Feiring (1946) found prolongation of the auriculo-ventricular conduction time in two cases of Reiter's syndrome Warthin (1948) noted variations in the T waves in one case consistent with a diagnosis of active myocarditis, treatment with streptomycin produced a "dramatic improvement"

It is well known that a similar syndrome may follow bacillary dysentery Paronen (1948) described 344 cases during an epidemic of Flexner dysentery 23 had myocarditis and pericarditis, sixteen myocarditis alone, and three pericarditis alone The carditis lasted for up to 5½ months and appeared as early as the first week of the disease or as late as the 32nd month

Lovgren and Masreliez (1949) encountered changes in the electrocardiogram in six out of 22 cases of Reiter's syndrome, and two additional cases with cardiac abnormalities were reported by Trier (1950)

Shapiro Lipkis, Kahn, and Heid (1949) described electrocardiographic changes in four female cases of acute gonococcal polyarthritis, which "demonstrate a pertinent exception to the axiom that polyarthritis plus an abnormal and unstable electrocardiogram is pathognomonic of acute rheumatic fever They consider that the electrocardiopathy is apparently caused by a "toxic by-product of the infecting organism (as suggested by Katz, 1946) rather than a true inflammatory lesion In two cases the electrocardiogram became normal in 1 month, one case left hospital against advice on the 17th day with a still abnormal electrocardiogram, and the fourth case continued to exhibit an abnormal record on the 39th day after treatment

Finally Harkness (1950) found tachycardia (120 to 150 per min) in two cases of Reiter's syndrome over a period of 5 to 6 weeks during the acute phase

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† Read before the M S S V D London on March 25 1955

Case Histories

Case 1, naval rating, aged 28, married, exposed himself to possible venereal infection on January 22, 1953 Five days later he developed a urethral discharge A urethral film showed Gram-positive and Gram-negative cocci and pus cells Treatment was started with procaine penicillin (300,000 units daily), but 4 days later buccal ulceration, pharyngitis, and bilateral conjunctivitis had appeared He was accordingly admitted to hospital as a probable case of Reiter s syndrome

Examination—On February 1 examination showed bilateral conjunctivitis with lacrimation and a mucopurulent conjunctival exudate, shallow white ulcers on the inside of the cheeks, the roof of the mouth, uvula, the anterior fauces, and the posterior pharyngeal wall, small circinate keratotic patches on the glans penis and undersurface of prepuce, but no other skin lesions, no arthritis A film of the urethral discharge showed numerous pus cells but no organisms, and a mid-stream urine specimen gave no growth on culture The prostate was slightly enlarged The erythrocyte sedimentation rate (Westergren) was 10 mm in the 1st hour, 26 mm in the 2nd hour The Wassermann reaction and the Kahn and gonococcal complement-fixation tests were negative

History—Gonococcal iritis and arthritis in 1943, urethritis and iritis in 1945, gonorrhoea twice in 1946, iridocyclitis in 1946, urethritis in 1948, Reiter s syndrome (balanitis, urethritis, conjunctivitis) in 1952, and clinical chancroid in 1952

Therapy—It was proposed to treat him by fever therapy (intravenous T A B vaccine) The results of the pre-fever investigation on February 3 were as follows

Blood urea nitrogen 10 mg per cent
Chest x ray Normal
Electrocardiogram Normal sinus rhythm Rate 65 per min P-R interval 0 16 sec The record was highly abnormal showing slight ST elevation and upright T waves in three standard leads, ST depression and inverted T waves in aVR, ST elevation and low upright T waves in aVF, ST elevation in all chest leads, most marked in V3, in V4 a 3 mm Q wave preceding a tall R wave, in V5 Q wave measured only 2 mm The changes recorded were those of sub-epicardial or pericardial damage with the most marked changes over the anterior surface of the heart The wide distribution of the ST/T changes suggested pericarditis The decreasing amplitude of the Q wave from V4 to V5 suggested localized sub-epicardial damage

Repetition of the electrocardiogram on February 10, 17, 24, and on March 5, 1953, showed no significant change in the above findings

Fever therapy was therefore not employed, treatment being by local instillations into the eye (albucid 30 per cent, atropine 1 per cent, cortisone) and anterior urethral irrigations In addition he received a course of 11 5 mega units crystalline penicillin G for furunculosis of the neck due to *Staphylococcus aureus* After 1 month in hospital he developed marked keratoderma blennorrhagica of the soles of the feet and the erythrocyte sedimentation rate was still elevated (9 mm in the 1st hour, 20 mm in the 2nd hour) He was then transferred to a convalescent unit where he made a symptomatic recovery

Later Developments—A year later, on January 17, 1954, he again risked extra-marital coitus and 8 days later exhibited dysuria, frequency, a urethral discharge, bilateral conjunctivitis, and injection of the buccal and pharyngeal mucosa with superficial ulceration The stained film of the urethral discharge revealed large numbers of pus cells and a few Gram-negative extracellular diplococci (morphologically resembling gonococci) The Wassermann reaction and the Kahn and gonococcal complement-fixation tests were negative The erythrocyte sedimentation rate was 6 mm in the 1st hour, 20 mm in the 2nd hour Culture of mid-

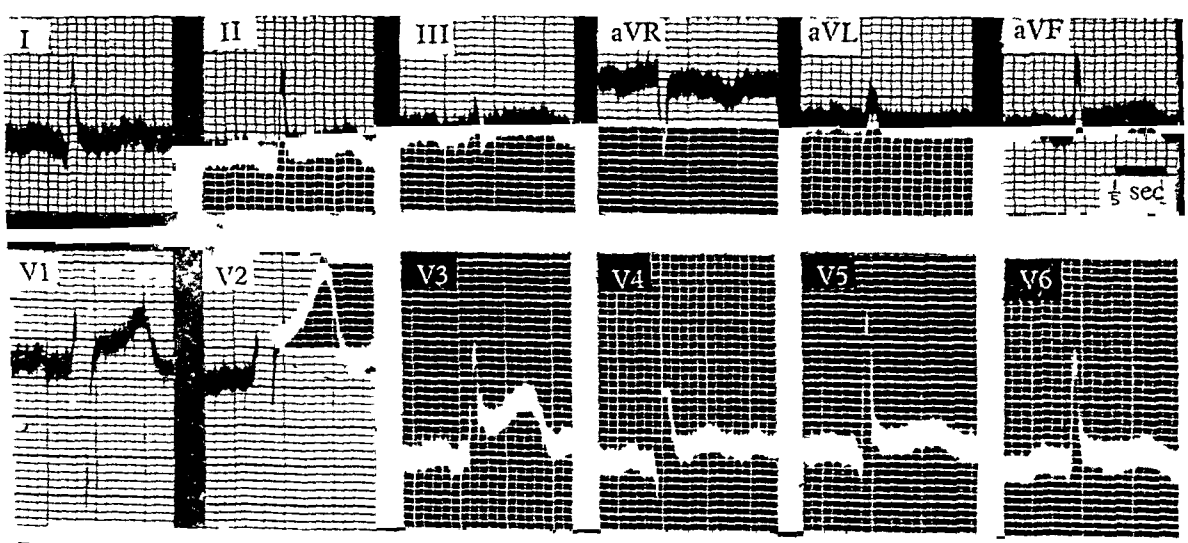

FIG 1—Case 1 illustrating changes suggestive of pericardial and sub-epicardial damage (Widespread ST elevation decrease in amplitude of Q wave from V4 to V5

stream urine gave a growth of Gram negative diplococci overgrown by diphtheroids A stained film of the conjunctival exudate showed pus cells but no organisms The blood urea nitrogen was 19 mg per cent

On January 27 the electrocardiogram was reported on thus

Comparison with the record taken on March 5, 1953 shows little change except that the T wave in V4 is now very shallow and inverted, and that the T waves in V5 and V6 are flat The ST shifts certainly suggest the presence of pericarditis and are very unusual

Again fever therapy was regarded as contraindicated and treatment consisted of saline eye baths, glycerine of thymol mouthwashes, crystalline penicillin G (200,000 units 4-hrly to a total of 6 mega units), and two courses of terramycin (20 g and 15 g respectively) Symptomatic recovery followed the second course of terramycin, but repetition of the electrocardiogram on February 11, March 8 and April 9, 1954 showed persistence of the abnormalities noted above

Case 2, physical-training instructor, aged 30, married, developed mild balanoposthitis on December 12, 1953 *There had been extra-marital coitus 2 weeks previously* He had no previous history of venereal disease Two days later a urethral discharge appeared and the left knee became painful and swollen A stained film of the discharge showed pus cells +++, Gram negative diplococci morphologically resembling gonococci+ Culture gave a growth of similar organisms but biochemical confirmation was not obtained The Wassermann reaction and the Kahn and gonococcal complement-fixation tests were negative A single injection of 600,000 units oily procaine penicillin was given

A week later there was no discharge and no pyuria, and a midstream urine culture was sterile The left knee was still painful however, and the erythrocyte sedimentation rate was 13 mm in the 1st hour, 23 mm in the 2nd hour On December 29 he was admitted for pre-fever investigation, which gave the following results

Clinical examination of cardiovascular system NAD
Blood pressure 124/80 mm Hg
Blood urea nitrogen 14 mg per cent
Chest x ray Normal
Electrocardiogram Normal sinus rhythm Rate 71 per min P-R interval 0 2 sec Horizontal heart The record showed the presence of anterior myocardial infarction with involvement of the septum

Accordingly fever therapy was regarded as contra indicated and treatment was restricted to local measures (radiant heat, kaolin poultices) X-ray examination of the left knee showed soft tissue swelling, with localized sub articular osteoporosis most marked in the peripheral areas The other joints were unaffected, but about this time slight angular conjunctivitis was noted in the right eye The prostate was normal on palpation and the prostatic fluid contained neither pus cells nor organisms

On December 12 repetition of the electrocardiogram confirmed the previous findings The erythrocyte sedimentation rate was 6 mm in the 1st hour, 11 mm in the 2nd hour Plasma fibrinogen was 0 8 g per cent A 24-hr specimen of urine tested for urobilinogen revealed a slight trace (not estimable ')

One month later the patient was discharged from hospital An electrocardiogram at this time was identical with the previous ones

Three months later an electrocardiogram was reported as follows

Comparison with the previous record shows steeper inversion of T in V3 T is flat in V5 and V6

After leaving hospital he felt perfectly well and resumed his previous occupation

Summary and Conclusions

Two cases of gonorrhoea complicated by Reiter s syndrome in young men are described In both cases the electrocardiogram was highly abnormal yet neither exhibited any clinical cardiovascular abnormality It is uncertain whether the relationship is significant or merely adventitous, but the ages

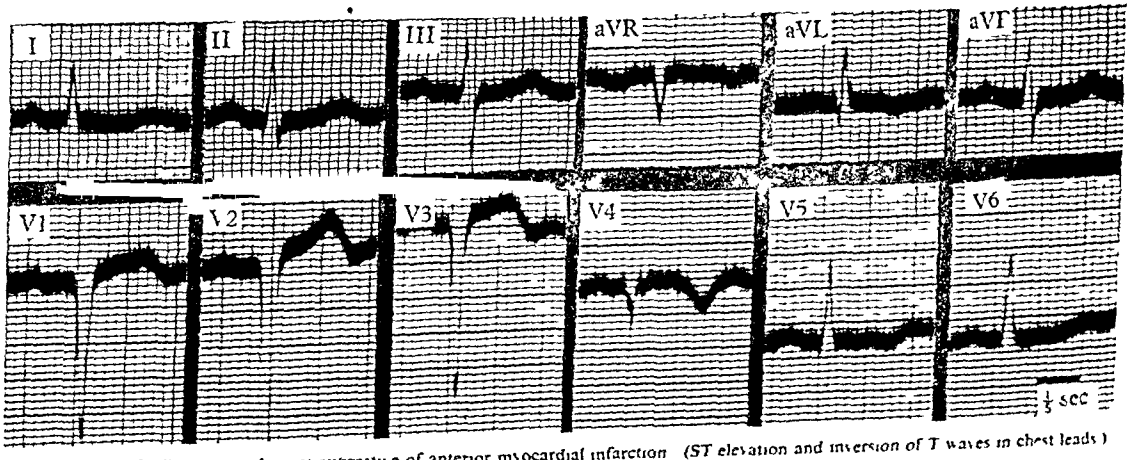

FIG 2 —Case 2 illustrating changes suggestive of anterior myocardial infarction (ST elevation and inversion of T waves in chest leads)

of the patients and the persistence of the electrocardiogram changes are quite unlike those found in coronary arterial disease

It is suggested that the changes in the electrocardiogram which have frequently in the past been ascribed to toxic gonococcal carditis are possibly a further manifestation of Reiter's syndrome, which may occur alone or as a complication of gonorrhoea It is further suggested that electrocardiography should form part of the routine investigation of all cases of Reiter's syndrome, whether or not fever therapy is contemplated, in an attempt to elucidate the problem

I wish to thank Dr Robert Lees for permission to publish this article I am also greatly indebted to Dr R M Marquis for his advice and to Mr Danskin for his technical help

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LATE CONGENITAL SYPHILITIC NERVE DEAFNESS*†

BY

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Ritchie Rodger (1945) speaking to this Society classified congenital syphilitic nerve deafness into early and late He gave two varieties of the early type, a neuritis associated with basal meningitis, and an oto-labyrinthitis These two early varieties were found to occur in infancy There is only one late type, a labyrinthitis, which is by far the commonest of all varieties, this usually occurs after the age of 9 years, but may appear at any period in adult life The following remarks apply to this late type only

The exact nature of the pathology of late syphilitic nerve deafness has never been settled There is still some support for the idea that the condition is caused by degeneration in the eighth nerve itself Degeneration of midbrain nuclei or pressure from inflammatory changes around the nerve have also been suggested *Post-mortem* material is, by the nature of the condition, not readily available Apart from a few individual reports there is only one collected series in the literature Mayer and Fraser (1936) described a serous labyrinthitis which they believed to be consequent on periostitis and osteitis in the bone surrounding the cavities and canals of the internal ear Microscopically, they believed the lesions to be miliary gummata There is no report that a search was made for *Spirochaeta pallida* This work has never been confirmed It is interesting to note that, although the patients described had had treatment, new and healed microscopic lesions existed side by side

Clinically, late congenital syphilitic nerve deafness is often total and of sudden origin In others it starts mildly and progresses rapidly or slowly Usually it is bilateral and is much commoner in females It often follows the occurrence of interstitial keratitis by some 2 or 3 years, or even longer In association with the deafness many patients complain of tinnitus, which may precede or follow deafness and be persistent Associated vertigo is not uncommon These patients usually have a strongly positive blood Wassermann, and invariably a normal cerebrospinal fluid The condition appears to be uninfluenced by antispecific treatment, and indeed deafness may occur during therapy, and even after what is generally regarded as adequate treatment

Some of the less dramatic cases bear a resemblance to Meniere's disease, in which vasodilator drugs have recently been used with varying success (Fisher and Tebrock, 1953) The reports give the impression that the exhibition of vasodilator drugs is worth a trial in every case Meniere's disease is another condition in which the pathology is obscure The consensus of opinion favours a labyrinthitis of vasomotor origin (Brunner, 1948), the vasomotor changes being due to allergy or hypersensitivity to some toxin which may be metabolic or infective in origin It will be remembered that Meniere s disease is manifest by progressive deafness, associated with attacks of tinnitus and vertigo The deafness usually worsens after each of the attacks, and in not a few cases the patient progresses to total bilateral nerve deafness

Is it possible that these two conditions, late syphilitic congenital nerve deafness and Meniere s disease, are in some way related? Is it possible that they have a common type of origin in hypersensitivity of some kind? If this were so, late congenital syphilitic nerve deafness would be placed in the same category as interstitial keratitis This would explain in some measure the failure of the condition to respond to antispecific treatment and its appearance or progress in spite of such treatment On these very theoretical grounds it was considered that a trial with vasodilator drugs might be worth while in syphilitic nerve deafness

Ronicol,* the alcohol of nicotinic acid the active principle being beta-pyridyl carbinol, was the drug used Ronicol produces gradual and prolonged vaso-

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† One of a series of short papers read to the M S S V D on April 29 1955

* Ronicol is manufactured by Roche Ltd

dilatation, has very few side-effects, and may be administered for long periods It is made up in 25-mg tablets Four cases of late congenital syphilitic nerve deafness are described below

Case Reports

Case 1, a female, aged 53, first attended in February, 1952, with iridocyclitis The Wassermann reaction was strongly positive and the cerebrospinal fluid normal There was no history or evidence of acquired syphilis The husband and three children were Wassermann reaction negative, and the patient stated that her mother had been fully treated for syphilis The patient gave a history of bilateral nerve deafness with head noises for only a few months before her initial attendance The condition had started with head noises, followed 3 weeks later by the onset of deafness She was examined by an aural specialist who diagnosed congenital syphilitic nerve deafness Full antispecific treatment was completed some 2 years after her initial attendance There was no improvement in the deafness Trial of Ronicol was started in November, 1954, using 25 mg three times a day At the end of a fortnight there was no change The dosage was increased to 50 mg three times a day, and after a further 2 weeks of this treatment the patient stated that the deafness was about the same, although occasionally voices sounded "very tinny The head noises were no better, but she stated that her attacks of dizziness were slightly less frequent Ronicol treatment was discontinued

Case 2, a female, aged 22, first attended in August, 1952, with antenatal Wassermann reaction positive There was a history of interstitial keratitis in 1943, when she received full and prolonged antispecific treatment Deafness commenced in 1948 and progressed rapidly From the beginning it was associated with severe head noises, and difficulty in balancing, especially in the dark There were no neurological signs, and the cerebrospinal fluid was normal Apart from an 'insurance" course of penicillin during the pregnancy, she had no further antispecific treatment Ronicol 25 mg three times a day was started in October, 1954, and continued for 14 days For the first few days the head noises were very much worse, and the patient had great difficulty in getting to sleep Thereafter the condition settled down, and at the end of a month, in spite of increasing the dosage, no change was noted

Case 3, a female, aged 40, whose mother had died of general paralysis of the insane There were no other members of the family She first attended in 1947 with a gummatous ulcer of the left shoulder and received about two courses of antispecific treatment before defaulting Bilateral deafness, associated with severe head noises and vertigo, first started in 1949 and advanced rapidly for 3 weeks In this case a hearing aid was of little value in view of the severe head noises Ronicol 25 mg three times a day was started in October, 1954 After a few days, the patient complained of flushing of the face There was no change in the deafness, vertigo was much the same, but she stated that the head noises were "not so bad'

In view of the face flushing, the dosage was reduced to ½-tablet three times a day, but the side-effects continued to be troublesome, and, although the tinnitus improved further, treatment was discontinued With the discontinuance of treatment, the head noises became as bad as previously Later, she asked for further supplies of the tablets, as she was in no doubt that they helped the head noises and made her hearing aid more useful

Case 4, a female, aged 35, first attended in April, 1952, with antenatal Wassermann reaction positive She had Hutchinsonian incisors She received two courses of penicillin and one of bismuth, and was transferred to care elsewhere after the birth of the baby, 16 months after her original attendance she was referred back by an aural specialist with a diagnosis of congenital syphilitic nerve deafness, which had started 4 months previously The patient had severe head noises, which seemed to be getting worse There were also attacks of dizziness Full antispecific treatment was completed in September, 1954, without any change in the patient's symptoms In October, 1954, Ronicol treatment was started (25 mg three times a day for 14 days) There was immediate improvement in the head noises, no change in the dizziness, but the patient thought her hearing had improved slightly, probably because the head noises had subsided There were no side-effects and the dosage was increased to 50 mg three times a day After a further fortnight the head noises and the dizziness were giving her no trouble There was definite and sustained improvement in the hearing She asked for further supplies of Ronicol, and has continued taking the drug for 6 months Tinnitus and vertigo have remained completely absent, and she has discontinued using her hearing aid and states that her hearing has improved

Discussion

This trial series is very small, and no firm conclusion can be based on the findings Apart from the fact that all the patients admitted to some change in symptomatology while taking Ronicol, only one showed changes which could be classified as improvement It is interesting to note that this case is the one of most recent origin Further trials would seem worth while especially in early cases

It may well be that the more recent the history of deafness the greater the hope of improvement

This raises the point that, so far, we are not able to tell which cases of congenital syphilis are liable to develop nerve deafness The pathological changes described by Mayer and Fraser (1936) suggest that bony changes may be present for some years before the onset of symptoms If we can find a method of detecting pathological changes in the ear before deafness has occurred we may not only be in a position to differentiate between congenital and latent syphilis but also may have an opportunity

to try to prevent deafness If the nerve deafness is a result of syphilitic periostitis with labyrinthitis, the microscopical changes being brought about by the presence of spirochaetes in the internal ear, then one may consider the use of vasodilator drugs as a useful adjunct to antispecific treatment, that is, with a view to concentrating drugs, for example, penicillin, at the site of the inflammation If, however, late congenital nerve deafness and interstitial keratitis are manifestations of the same hypersensitivity, and akin to Meniere's disease, then one will have to consider whether vasodilator drugs are likely to be useful, or whether cortisone, or cortisone-like treatment, *e g* , fever therapy, or prolonged aspirin treatment, should be tried

Congenital syphilis is becoming less common We have, however, to deal with a back-log of cases It is likely that some 10 to 15 per cent of the late congenital syphilitics will present with, or subsequently develop, nerve deafness It is now nearly 100 years since Hutchinson (1863) described his triad The notched incisors which he described have never been a problem If found aesthetically unacceptable to the patient (or her medical attendant), they can be extracted and replaced by a prosthesis Interstitial keratitis we can now control almost completely with topical cortisone The time seems ripe to turn our attention to the third component of the triad, and these few thoughts on the subject are, therefore, advanced for consideration

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GONORRHOEA IN A CASE OF CONGENITAL ABSENCE OF THE VAGINA*

BY

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As we have been unable to trace any reference to urethral gonorrhoea in a patient who has an atresia or absence of the vagina, we consider the following case worthy of note

Case Report

An unmarried white girl aged 20 attended our Clinic on November 8, 1954 She gave a history of perineal discharge, and of frequency and burning of micturition for 1 week She stated that for the past 6 months she had been having regular 'intercourse" with a soldier, who had told her that he was having treatment for gonorrhoea at another centre Intercourse had always been painful and difficult for the patient She had never menstruated

Examination.—The patient was a normally developed girl for her age Her labia majora were normal The clitoris was very small Her labia minora appeared to be undeveloped and atrophic The urethral orifice was inflamed, and the purulent discharge had spread, matting the pubic hair

The vaginal orifice was replaced by an indentation about $\frac{3}{4}$ in deep which was covered with clinically normal skin No uterus or cervix could be felt on rectal examination

Cultures from the urethral orifice gave ready growth of *Neisseria gonorrhoeae* The gonococcal complement-fixation and Kahn tests and the Wassermann reaction were negative

The urethritis responded readily to systemic penicillin treatment, and recovery of the patient was uneventful

We are grateful to Dr R M Heggie for the bacteriological examination, and to Mr G S Sturtridge for gynaecological confirmation of the anatomical defect

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ORIGIN OF GONORRHOEA AND NON-SPECIFIC URETHRITIS*

BY

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Rolleston (1934) showed that syphilis did not exist in ancient Greece and Rome Although he stated that there is no reference to venereal disease in classical literature, in the Arabian Nights, Villon, or Boccaccio's "Decameron", he rather lamely accepted the well-known passage in "Leviticus ' as an indisputable reference to gonorrhoea, and thought that in the prevailing squalor the symptoms and signs passed unnoticed for a thousand years

More recently Dr H St H Vertue (1953) re-opened the subject with a masterly and even more complete review of classical literature His article may be summarized as follows

It is generally believed that gonococcal urethritis or gonorrhoea is as old as man, or at least originated in the promiscuous squalor of the ancient eastern civilizations But not a single mention of the disease can be found in a search through classical, general, and medical literature from the times of Hippocrates to Galen and later The most cogent arguments of all are perhaps that Juvenal does not note it in any of his sixteen satires, and that Galen, a very acute observer, also fails to describe it Actually Galen (2nd cent) did mention gonorrhoea, but defined it as an unwanted excretion or seeping of semen Later the Greek word, which means exactly this, was wrongly applied to a contagious urethritis, which probably arose during the late Dark Ages According to Beckett (1717-18 1720) this was first described by John of Arderne (about 1380) as a burning inflammation (*incendium interius*), and by another 14th century writer whose manuscript (1390) was in Beckett s possession as Brenning of the Pyntyl, yat Men call ye Apegalle , it was mistakenly identified with Galen s gonorrhoea by those who could not believe that the master would have missed or omitted it Galen s famous contemporary Aretaeus of Cappadocia (2nd cent) likewise described a persistent flow of semen but it is equally impossible to read into this what we mean by gonorrhoea Celsus in the first century A D wrote in the same vein ' There is a fault in the genital region called a shedding of semen It occurs without sexual desire or erotic dreams, and in such a way that after a time the patient is consumed with wasting '

Vertue found no mention of contagious urethritis in the writings of Hippocrates or in classical Greek literature , the freely quoted passage in 'Leviticus , XV ' When any man hath a running issue out of his flesh', surely must not be misconstrued from the general to the particular , nor is Horace s or Ovid's carefree world of courtesans and brothels marred by a single reference to venereal disease The inescapable conclusion is, therefore, that venereal disease just did not exist in the classical world To carry the matter still further, we find that the great Arabian masters, Rhazes, Avicenna, and Avenzoa, also make no mention of the disease as being in existence in the Dark Ages (To this formidable array of classical writings may be added Apuleius s ' *The Golden Ass* ' (2nd cent) and Suetonius's ' Lives of the Twelve Caesars " (2nd cent) in neither of which is there any reference to venereal disease)

The first appearance of gonorrhoea, as we understand it, was probably in early medieval times, but it could not have been prevalent for a century or so, as there is no hint of it in the works of Chaucer, Langland, or Gower , in the Arabian Nights, in Villon's works, or above all, in the "Decameron (first edition, Venice, 1471) By 1430, however, the Bishop of Winchester was legislating that no stewholder in his Thames-side domain was to retain a woman that had the sickness of brenning under the extremely severe fine, for those days, of one hundred shillings ' By the late sixteenth century it is commonly mentioned or alluded to and had a new name bestowed upon it, namely ' clap It was a feared hazard of promiscuity as is seen in the Mirror for Magistrates (1587)

> They give no heed before they get the clap
> And then too late they wish they had been wise

But gonorrhoea was relatively so new that when syphilis appeared hard upon its heels the two were confused

> Time that at last matures a clap to pox
> Whose gentle progress makes a calf an ox (Pope, 1735)

and so remained through Hunter s day and until Ricord (1838) at last separated the two diseases

Vertue s survey convinces one that venereal disease in the main—syphilis and gonorrhoea—did not exist in ancient Greece and Rome, but what of the explanation of the condition described by Galen, Aretaeus, and Celsus—namely *Profusio Seminis* ? Such a condition cannot be identified with the defaecatory prostatorrhoea that worries a few young men, for this is not a persistent discharge , nor does such a semenorrhoea occur today

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as a symptom of neurasthenia May it not then refer to non-specific or abacterial urethritis? This quiet urethral inflammation comes on some 10 to 20 days after exposure to risk, and the true origin of the disease could easily have been missed in times when incubatory periods had not been recognized In this connexion it is noteworthy to remember that the venereal origin of syphilis was not recognized for many years

I therefore addressed the following letter to Dr Vertue

I read with very great interest your recent article on the history of gonorrhoea and congratulate you on a masterly, personally conducted, review of classical literature—a splendid feat of scholarship I became convinced that neither syphilis nor gonorrhoea existed in ancient Greece and Rome, but I cannot accept the explanation given for the *Profusio Seminis* described by Galen, Aretaeus, and Celsus, namely that this condition is a semenorrhoea or prostatorrhoea, a nervous disorder, or a sign of neurasthenia In thirty years of practice I should have had ample opportunity to see such cases if they occurred Granted one does see many cases of prostatorrhoea, usually in young men who come to the clinic complaining of a discharge yesterday or last week, frequently associated with the act of defaecation, but never as described by the classical masters

(1) It is possible that the condition no longer occurs This is most unlikely though diseases do alter and even disappear

(2) The symptoms may have been exaggerated by Galen whose account was copied by subsequent writers, but Aretaeus was a contemporary who did not have access to Galen's writings

(3) It would appear far more likely that these are descriptions of the signs and symptoms of non-specific urethritis which has only recently attained grudging recognition as an entity

The delayed onset of this quiet type of inflammation would have effectively masked its venereal origin It is, of course, difficult to fit in the "wasting" mentioned by Celsus, but any continued discharge when construed as "waste of seed" would induce a concomitant anxiety state

Dr Vertue replied

I am grateful for the opportunity here given me of elucidating a little further the meaning and nature of the ancient 'gonorrhoea" or "spermatorrhoea" The popular, not the scientific, beliefs in the matter were briefly these The seat of the seed, *sperma*, is in the brain, marrow, knees, and thighs, whence it passes into the bladder, the testicles being simply reservoirs The seed breathes through the external genitalia and being endowed with life yearns for emission that it may enter another and procreate The principle of life is the soul, *psyche*, and this is enclosed in the seed therefore in the seed is the very life itself (Plato, "Timaeus') In Latin the notion is the same, with the exchange of *genius* for *psyche* and *semen* for *sperma* It is no wonder, then, that the sufferer who believed that his seed was running away complained that he was exhausted, that his limbs were refusing their functions, and his knees giving way, nor that he might lose his reason or even pine away from superstitious terror What the old writers are describing as "gonorrhoea" or "spermatorrhoea" is a severe "anxiety state," which they named after the symptom most prominent in the patient's own account Even down to recent times fathers would strike horror into their sons by recounting the awful results of excessive loss of semen Many medical books used to contain references to this disorder Impelled by curiosity, I have examined a large American catalogue for the year 1911, that of the library of the Surgeon-General of the U S A No less than a page and a half are occupied by the list of articles on spermatorrhoea, and there is mention of a special institute at Boston devoted to the cure of it In the First World War I myself was consulted by soldiers, "neurasthenics", about this complaint and verified the truth of what they told me by examining the discharge under the microscope and finding spermatozoa But the forms of neurosis are determined by the way in which patients regard themselves and are regarded by society now that the outlook on sex is saner, spermatorrhoea is passing away One psychiatrist tells me that anxious young men still complain of it, but another has the very opposite experience Venereologists apparently seldom see it now, though Harkness (1950) mentions a spermatorrhoea, which must be distinguished from urethritis

My own conclusions on the subject are simply these The description of "gonorrhoea" or "spermatorrhoea" given by the ancients is a true account of a neurosis, unconnected with venereal disease, which has been in existence down to recent times but is now much on the wane On the other hand no reasonable man should deny the possibility that a non-specific urethritis may have been in existence and may have been confused with spermatorrhoea, even though actual unmistakable evidence is wanting

In my view the grim warnings on the effects of excessive loss of semen mentioned in Dr Vertue's letter were meant to curb or stop masturbation, and I still remain somewhat sceptical regarding spermatorrhoea The review of classical Greek and Roman literature strongly indicates (though it *cannot* prove) an absence of gonorrhoea (and syphilis) in that Golden Age There is nowhere a single reference to the typical inflammation and discharge of gonorrhoea, to stricture, or to ophthalmia neonatorum But "Leviticus", XV, cannot be dismissed easily Dr Vertue considers that "an issue out of his flesh" refers to discharges from wounds and abscesses, but in fact the whole chapter is exclusively devoted to genital discharges in men and women, discharges which the Jewish Elders knew to be infectious and on account of which they made scrupulous rules of hygiene There is even a distinction made between this infectious issue and the

running of " the seed of copulation," *i e*, true spermatorrhoea If the urethritis had been gonorrhoea it could not have long remained a Biblical scoop But if the description in vv 2–18 does not refer to gonorrhoea at least it must indicate the presence of the less spectacular non-specific urethritis in Egypt and Israel in the days of the Old Testament

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PRELIMINARY AGGLUTINATION EXPERIMENTS WITH *TREPONEMA PALLIDUM**†

BY

G EHRMANN AND H Aa NIELSEN

From the Statens Seruminstitut, Copenhagen, and the Klinik für Geschlechts- und Hautkrankheiten, Vienna

Nelson and Mayer (1949) demonstrated the action of immobilizing antibodies on mobile and virulent *Treponema pallidum in vitro* These antibodies do not only immobilize but also destroy treponemes exposed to such antibodies in the presence of complement lose their motility and also their virulence and their ability to multiply However, as the first obvious manifestation of the antigen-antibody reaction was the loss of mobility of the treponemes, the reaction by which they were demonstrated was described as the *Treponema pallidum* Immobilization (TPI) test

It was natural to try to demonstrate other specific antibodies against virulent *Treponema pallidum* Studies of specific immobilization *in vitro* will reveal that many specific immobilized treponemes are not only immobile, but also appear to have changed morphologically as if they had been "chafed" or "gnawed" Frequently, there is also a visible diminution in the number of organisms The adherence disappearance reaction developed by Nelson (1952) may be due, at least in part, to a specific lysis

Living, mobile treponemes are known to have a tendency to form agglutinates in certain circumstances In our experiments we have also seen that the agglutination of *live* treponemes may occur in the absence of antibodies in the serum Further, we know that physical factors, such as shaking, or merely sedimentation, will agglutinate treponemes However, Cain (1953), McLeod and Magnuson (1953), Tani and Asano (1951), and Hardy and Hollander (1953) succeeded in suspending *dead* treponemes in such a way that they did not agglutinate spontaneously, even after having been left for weeks at −4° C, or after shaking This made it possible to repeat experiments with the same antigen and to make adequate tests of reproducibility This and the independence of complement are the two great advantages of this method However, the fact that no complement is necessary for the agglutination reaction is also a drawback of agglutination tests if the results are intended for diagnostic use, because there is no satisfactory means of controlling the potential presence of non-specific agglutinating factors in the serum If, however, a diagnosis of syphilis has been established, the consistent demonstration of agglutinins also opens up new possibilities in syphilis research

The following investigations were inspired by such theoretical considerations and by the papers published by McLeod and Magnuson, by Cain, and by Hardy and Hollander on the *Treponema pallidum* Agglutination reaction (TPA) test We wanted to compare the reproducibility, the sensitivity, and the specificity of the TPA test with those of TPI tests and of the old tests with lipoidal antigens by which the so-called reagins are demonstrated (reagin reactions)

Methods and Material

At the Statens Seruminstitut in Copenhagen we examined 194 sera, mostly human, for the presence of three groups of antibodies immobilins, agglutinins, and reagins

The TPI test (H Aa Nielsen) was carried out in its latest form as described by Nelson and Mayer (1949), the only modifications being a four-fold increase of the sodium thioglycollate content of the medium and the taking of readings after 18 and 42 hrs' incubation In the latter case complement was added twice, *i e*, immediately and after 24 hrs' incubation, the final contents of complement being the same as that employed in the 18-hr experiments

Reagins were demonstrated by Meinicke's clarification test, Kahn's Standard test, and Morch's complement-fixation test with cardiolipin antigen (MR, KR, and C-WR-M)

For TPA tests (G Ehrmann) as well as for TPI tests we used the pathogenic Nichols strain inoculated intratesticularly in rabbits In order to avoid *in vivo* presensitization of the treponemes, the rabbits had been irradiated on the same day or the day before inoculation. Rabbits weighing about 3 kg were given a single universal radiation of about 1,000 r Data Focal distance 40 cm Filter 0 5 Cu, 1 0 Al, 215 kV 10 mA The thinly sliced testes with early orchitis were shaken in a 0 85 per cent saline solution Each testis was shaken

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† The experiments reported in this paper were carried out in Copenhagen in December 1953 and January 1954 during a study visit made possible by the World Health Organization

in 20 ml saline three times for 30 min at +4° C The suspensions obtained were poured together after completion of shaking A considerable amount of tissue debris, erythrocytes, and sperma was removed by 10 minutes' slow centrifugation The clear suspension was then centrifuged for 60 min at 3,000 rotations per minute in a centrifuge of 20 cm radius The sediment was washed once with saline, diluted to 10 to 15 million organisms per ml of saline, and killed by heating in a water bath at 56° C for 30 min Suspensions prepared in this way showed spontaneous agglutination in three batches out of twelve The satisfactory suspensions were kept at +4° C ready for use during the whole period of the experiment (4 weeks) During our attempts to prepare a reliable suspension we made the following observations

The testes were carefully prepared and were freed from fat, because fat contents will give rise to agglutinates Such agglutinates, which may be distinguished from specific ones, may cause a loss of treponemes and impair the readings This applies also if the preparation is shaken too fast, and if the work is performed at higher temperatures than about 4° C Removal of tissue particles by filtration through coarse glass filters and through filter paper was not successful

Apparently, morphologically damaged treponemes will adhere to the glass, this may frequently be observed when placing treponemes on slides, and will often result in a very undesirable loss of organisms—sometimes almost 100 per cent Equally unsatisfactory results were obtained in attempts to kill the treponemes with penicillin Thus agglutination with treponemes prepared in this manner is completely non-specific, even if the organisms retain their form better than when they are killed by heating

It was found that the addition of merthiolate, as recommended by Hardy and Hollander (1953) was not necessary for the preservation of the treponemes Finally, it was observed that several treponemal suspensions did not show any *in vivo* sensitization in the TPI test in spite of the fact that they did agglutinate spontaneously

Technique —Normal agglutinins were removed from human sera by means of sheep cells Inactivated serum 1 ml and 2 ml 50 per cent sheep cell suspension in saline were thoroughly mixed and left in a water bath at 37° C for 90 min and then placed in an icebox for 18 hrs at about +4° C The sheep cells were subsequently removed by centrifugation

Absorbed serum 0 025 ml + antigen suspension 0 1 ml were shaken for 2 hrs in a covered Kahn shaker, causing a rise in temperature of 28 to 30° C The mixture was left in a water bath at 45° C for 8 to 12 hrs Antigen suspensions alone, without serum, were always used as controls

Readings —Without previous shaking, 0 01 ml of the sediment was removed with a special pipette and examined in dark field The agglutinates were first identified in low power, and then, in a higher magnification (× 512), identified as "genuine" agglutinates The treponemes had by then settled lengthwise end to end, forming pointed, spiral-shaped bundles of variable thickness which, by strong agglutination, again assembled into larger groups The characteristic *spiral shaped serrations and striped appearance of the agglutinates distinguish them from the pseudo agglutinates*, in the latter agglutinates the treponemes form loose balls, mostly with an amorphous centre

Counts were made of 25 fields, the agglutinates thus identified were recorded in such a manner that the number of treponemes per agglutinate could be evaluated and averages calculated At the same time, the number of free treponemes in the fields were counted Three values were thus obtained for each serum

(1) Number of agglutinates in 25 fields,
(2) Average number of treponemes per agglutinate
(3) Number of free treponemes in 25 fields

A positive value was defined as having at least one agglutinate with ten or more treponemes observed in each of the 25 fields The third figure served as a control reading, the result necessarily depending upon the first two figures The more numerous the agglutinates and the higher the average of the agglutinated treponemes the fewer were the free treponemes and *vice versa*

In this manner 154 human and forty rabbit sera were examined, the results were compared with those obtained by the reagin reactions and TPI tests

Of these, fifty (three rabbit and 47 human sera) were taken from the stock of lyophilized sera kept at the Statens Seruminstitut in its capacity of WHO Reference Laboratory, the remaining 107 human sera were taken from the TPI routine, and the remaining 37 rabbit sera originated from various experiments set up for other purposes

Results

(A) **Human Sera** —The sera were divided into four clinical groups

Group 1 —43 sera from 37 patients with definite anamnestic and clinical syphilis, all the patients of this group had been treated, several of them for many years

Group 2 —Fourteen sera from fourteen patients with doubtful syphilis Most of the patients from this group had been treated As the results for Groups 1 and 2 were very much alike, they were compiled together (Table I)

TABLE I

GROUPS 1 AND 2 DEFINITE AND DOUBTFUL SYPHILITICS (57 SERA FROM 51 PATIENTS)

Combined Result of Reagin Reactions	Reagin Reactions	TPI		TPA
		18 hrs	42 hrs	
+ and ±	39	41	43	41
−	18	16	14	16

Group 3 —35 sera from 34 patients in whom the possibility of syphilis could be excluded with almost

TABLE II

TWELVE CASES WITH DISCREPANT RESULTS

Case No	Combined Result of Reagin Reactions	TPI_{18}	TPI_4	Clinical Findings	TPA	Time of Diagnosis	Whether Treated
1	−	−	−	Dark field positive primary syphilis	+	1948	Yes
2	−	+	+	Dark field positive primary and secondary syphilis	−	1951	Yes
3	±	−	−	Dark field positive primary syphilis	±	*1 month ago*	Yes
4	−	±	±	Dark field positive secondary syphilis	−	6 months ago	Yes
5	±	±	±	Aortitis	−	1939	Yes
6	−	+	+	No information on stage of disease	−	About 1924	Yes
7	−	±	+	,	−	1918	Yes
8	−	±	−	, ,	−	1947	Yes
9	±	−	±	,	−	1952	Yes
10	±	−	−	Doubtful congenital syphilis Observed for non specific reactions	−	1949	Yes
11	±	−	±	Doubtful secondary case	−	1949	Yes
12	−	−	−	Herpes genitalis Reagin tests strongly positive at diagnosis	−	1950	No

complete certainty In this group only a few patients had been treated

Group 4—Control group comprising 62 sera from healthy blood donors

The results of the three reagin reactions C-WR-M, KR, and MR are listed as "combined results" +, ±, and − in Tables I, II, and III, taking the degree of conformity between the reactions and the strength of the reactions into consideration In other words, a ± result may signify the result of three weak reactions or of two strongly positive reactions and one negative reaction

The summarized results given in Table I show that the three types of reactions (reagin reactions, TPI, and TPA) seem to agree fairly well There were, in fact, twelve sera from twelve treated patients in whom discrepant results were found These findings are given in Table II

In presumably non-specific cases (Group 3) both TPA and TPI showed significantly fewer positive (+ and ±) reactions than the reagin tests ($P < 1\ ^0/_{00}$)

TABLE III

GROUP 3 NON SPECIFIC CASES? (35 SERA FROM 34 PATIENTS)

Combined Result of Reagin Reactions	Reagin Reactions	TPI		TPA
		18 hrs	42 hrs	
+ and ±	30	8	8	13
−	5	27	27	22

Results of the five positive cases in TPA, which were not positive in TPI, are listed in Table IV

No significant difference could be demonstrated between the TPI and TPA tests

In the controls (Group 4) the TPI and TPA reactions were negative in all sera, whereas three sera reacted in one or more of the reagin tests

	C-WR-M	KR	MR
(1)	—	Non-readable	±
(2)	—	—	+
(3)	—	Non-readable	—

(B) Rabbit Sera—Sera from normal rabbits as well as from rabbits inoculated intratesticularly with the pathogenic Nichols strain of *Treponema pallida* were tested Sera from rabbits immunized

TABLE IV

TPA POSITIVE TPI NEGATIVE SERA

Case No	Symptoms	Test			Combined Result
		C-WR-M*	KR*	MR*	
1	Retinopathy hypertension	—	1	—	±
2	Lupus erythematosus	11	8	+ —	±
3	Simple ulcer of the labia pudendi Lesion healed up in 2 days after local treatment with mercurochrome No glandular swelling No induration	—	—	—	—
4	Rheumatoid arthritis	1	2	— —	—
5	Pregnancy arthritis pulmonary infiltration	1	2	— —	—

*The results of C-WR-M and KR are given in degrees of strength (Schmidt 1951) The MR results are listed in the usual way strongly positive (— —) weakly positive (—) doubtful (±) and negative (—

TABLE V

RESULTS OF RABBIT SERUM TESTED BY TPI BEFORE (SERUM NO 1) AND AFTER (SERUM NO 2) INOCULATION WITH *T PALLIDA*

Rabbit No	Serum	TPI_{18}	TPI_{4}	TPA	C-WR-M	KR	MR	Combined Result	Time in Days from Inoculation	X ray
8255	1*	−	−	−	−	−	−	−		
	2*	−	−	+	4	1	+	+	13	1000 r
8256	1	−	−	−	−	−	−	−		
	2	−	+	+	15	12	++	+	15	1000 r
8310	1	−	−	−	−	−	−	−		
	2	−	±	+	10	9	++	+	9	−
8311	1	−	−	−	−	−	−	−		
	2	−	−	+	−	1	±	±	8	−
8312	1	−	−	−	−	−	−	−		
	2	−	−	−	−	−	−	−	6	1000 r
8314	1	−	−	−	−	−	±	±		
	2	−	−	+	7	5	++	+	8	−
8318	1	−	−	−	−	−	±	±		
	2	−	−	+	5	1	+	+	6	−
8319	1	−	−	−	−	−	±	±		
	2	−	−	−	4	3	++	+	7	−

* Serum No 1 withdrawn before inoculation Serum No 2 from 6 to 15 days after inoculation

against various bacterial diseases were also included in the experiments

(1) Three pools of serum from apparently healthy rabbits with weakly positive reagin reactions were negative in both TPI and TPA tests

One pool from thirty rabbits infected 4 months previously (WHO TPI Control No 2) was positive in all three types of reactions

(2) Serum was tested in eight rabbits from the TPI routine before (Serum No 1) and after inoculation with *Treponema pallida* (Serum No 2) The rabbits were not treated The results of the three types of reaction, time from inoculation, and information on *x*-ray treatment are given in Table V

All No 1 sera (except three with doubtful reagin tests) were negative in all three types of reaction TPI_{18} was positive in one No 2 serum only, and TPI_{12} was positive in the same serum and doubtful in another No 2 serum

TPA was positive in six out of the eight No 2 sera, and the reagin tests were positive or doubtful in seven out of the eight No 2 sera

(3) In an experiment set up for other purposes fifteen rabbits were infected intratesticularly with syphilis on May 5, 1952 Six weeks after inoculation all except one were treated with either penicillin or trepopal Altogether twenty sera from these fifteen rabbits were tested (Table VI) It should be noted that all the TPA and all the TPI_{12} results originate from one experimental day, the TPI_{18} results are taken from different days This fact accounts for the discrepancies between the results obtained for 18 and for 42 hrs, for which the day-by-day variations of the TPI test are responsible

(4) Nine sera from nine rabbits immunized against typhoid fever, and two sera from rabbits immunized against leptospirosis were all negative in both TPI and TPA

Discussion

Most of the strongly positive and clearly negative sera were examined once more in the TPA test As was to be expected, the results showed no change This good reproducibility was also attained in the probable, non-specific, positive cases of rheumatic fever and lupus erythematosus which were examined a few times and always showed the same weak but clearly positive results

With regard to the sensitivity of the TPA test in comparison with that of the TPI test and the reagin reactions, altogether twelve discrepancies were found in 57 human syphilitic sera (Tables I and II) In syphilitic rabbit sera a relatively large number of positive agglutination reactions were found (Tables V and VI), especially when compared with the TPI test

The introductory remarks about the specificity of the TPA test were confirmed by our experiments (Table III) The fact that one-third of the sera can agglutinate treponemes by non-specific normal agglutinin (Turner, 1953) shows that the test may take a non-specific course These probably non-specific results from sera of patients suffering from rheumatoid arthritis and lupus erythematosus are due to an agglutinating factor which is already being

TABLE VI

RESULTS OF TWENTY SERA FROM FIFTEEN RABBITS INFECTED WITH SYPHILIS ON MAY 5 1952

Rabbit No	Blood with drawn	Treat ment	TPI_{18}	TPI_4	TPA	C-WR-M	KR
156	Nov 26 1952	None	+	+	+	—	3
167	Nov 1, 1952	Penicillin	±	−	+	—	1
	July 24, 1953	Penicillin	−		+	—	1
168	July 24, 1953	Penicillin	−	−	+	1	2
170	Nov 1 1952	Penicillin	±	−	+	—	6
	July 24 1953	Penicillin	−	−	+	5	6
172	Nov 1, 1952	Penicillin	−	−	+	—	1
	July 24 1953	Penicillin	−	−	+	—	1
173	July 24 1953	Penicillin	−	−	+	—	1
175	July 24, 1953	Penicillin	−	−	+	—	—
179	July 24 1953	Penicillin	−	−	+	—	1
180	July 24 1953	Penicillin	−	−	+	—	1
182	Nov 24 1952	Trepopal	+	+	+	—	2
	July 24 1953	Trepopal	±	−	+	—	1
183	July 24 1953	Trepopal	−	−	+	—	—
185	July 24 1953	Trepopal	−	−	+	2	6
186	July 24 1953	Trepopal	−	±	+	—	—
190	July 24 1953	Trepopal	−	−	+	—	1
195	Nov 24 1952	Trepopal	−	+	+	1	4
	July 24 1953	Trepopal	−	−	−	—	2

used for serological diagnosis of rheumatoid arthritis (Ehrmann, Ferstl, Neumayer, and Schmidt, 1952) For this reason, and because of the difficulty of obtaining definite controls for non-specific agglutinins, we shall probably have to forgo the agglutination test in its present shape as a diagnostic aid, especially as the TPI test yields good specific reactions that so far are unsurpassed On the other hand, the TPA test may be helpful, as mentioned above in the further research of syphilis pathology and consequently also in the prognosis and evaluation of therapy

Summary

In 194 sera (154 human and forty rabbit) the results of a *Treponema pallidum* Agglutination (TPA) test, using heat-killed pathogenic treponemes, were compared with the results obtained in the *Treponema pallidum* Immobilization (TPI) test and in three different reagin reactions

The material comprised definite and doubtful syphilitic sera, presumably biologically false positive sera and normal sera This limited material did not allow any definite conclusions as to the sensitivity and specificity of the TPA test

In presumably biologically false positive sera both TPA and TPI tests gave significantly fewer positive results than the reagin reactions However, there was no significant difference between the TPA and the TPI tests in these sera

In syphilitic rabbits, agglutinins appeared almost simultaneously with reagins, the TPI test being preponderantly negative On the other hand, the TPA test remained positive longer than the TPI, the reagins lying somewhere between the agglutinins and immobilins

Non-specific normal agglutinins may also produce agglutination which could not always be removed entirely by absorption with sheep cells Presumably non-specific, positive TPA was obtained in rheumatoid arthritis and lupus erythematosus in spite of absorption

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AN APPRECIATION OF PRICE'S PRECIPITATION REACTION IN THE SEROLOGICAL DIAGNOSIS OF SYPHILIS*

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INTRODUCTION

The precipitation reaction for the diagnosis of syphilis (PPR), introduced by Price in 1948, has been widely used in Great Britain, but few reports have so far been published evaluating the test as a diagnostic procedure (Singh and Sharma, 1951, Wilkinson, 1954, Evans, 1954)

Since April, 1953, this laboratory has been using it in parallel with the Wassermann (WR) and Kahn reactions as a battery of tests for the routine examination of sera, and 16,000 tests, including 716 positive in some degree, have now been performed This paper analyses the results obtained and the value of the PPR with regard to sensitivity and specificity, both alone and in combination with the other reactions

MATERIALS AND METHODS

Antigens—Antigens for the Wassermann, Kahn, and PPR have been supplied throughout by the Venereal Disease Reference Laboratory (VDRL) through the courtesy of Dr I N O Price The VDRL titre has been accepted in every case

Complement—Preserved complement obtained from the VDRL has been used generally but occasionally freeze-dried complement (' Lyovac) has been substituted Complement titrations have followed the method of Price (1949b)

Haemolysin—This has been obtained commercially The titre is established for each bottle, and it has been shown to remain constant under good storage conditions

Sheep Red Cells—Defibrinated, formalized sheep blood has been obtained commercially Cells over a week old have not been used

Kahn Test—The method employed has been that of Kahn (1928) save that the 3 1 serum/antigen tube has been omitted and an autoflocculation tube substituted In addition, the serum has been pre-pipetted (Khairat 1952)

Price's Precipitation Reaction—Price's technique (1948) has been followed in its entirety except for reporting We have not used the method of units, quantitative results being expressed as the serum dilution only

Wassermann Reaction—The modifications introduced by Price (1950) have been followed

Sera for Test—Most of the specimens tested were sent to us by post, the serum having been separated before dispatch to us Specimens obtained locally are normally submitted as whole blood, and the serum is separated immediately upon receipt Since January 1954, sera sent by post have been merthiolated (Croft and Smith, 1946) Our method has been to evaporate 0 5 ml of 1 1000 tincture of merthiolate (Lilly) in bijou bottles at 60° C Because there is some evidence that merthiolate loses its potency with time, the prepared bottles have been distributed at weekly intervals to hospital laboratories As nearly as possible 2 5 ml of serum has been added to the bottle giving a final concentration of 1 5000 merthiolate in undiluted serum Pending testing, sera have been stored at −20° C, inactivation being undertaken immediately before performing the flocculation tests The two flocculation tests have been performed simultaneously twice weekly, the Wassermann reaction being done on the following day Thus at the most 4 days have elapsed between receipt of sera and completion of the tests

Reading of the Tests—No quantitative Kahn test has been performed, the Kahn being reported as positive or negative All positive PPRs and WRs have been titrated

ORIGINS OF THE SERIES

The results reported are from 16,000 consecutive sera submitted to this laboratory between April, 1953, and April, 1955, on which a report on all three tests could be given Specimens in which one or both of the flocculation tests showed autoflocculation or in which the WR was anticomplementary have been excluded Most of the sera are from Royal Air Force personnel and their families stationed or admitted to hospital in the United

* Received for publication June 8 1955

TABLE I
ORIGINS OF THE SERIES ARRANGED ACCORDING TO ORIGINAL DIAGNOSIS

Diagnosis	Number of Cases		
	Negative by All Tests	Positive by One or More Tests	Total
History unknown	1 117	36	1 153
Routine examinations	1 970	31	2 001
Antenatal cases	2 226	21	2 247
Neurological and psychiatric cases	2 500	26	2 526
Blood donors	823	30	853
External genital lesions	355	24	379
Clinical diagnosis of congenital or secondary syphilis	12	8	20
Treated syphilis — unknown stage	116	51	167
Treated syphilis — primary	153	26	179
Treated syphilis — secondary	47	25	72
Treated syphilis — tertiary	2	7	9
Treated syphilis — latent	28	132	160
Treated syphilis — congenital	5	110	115
Treated syphilis — neurosyphilis	2	22	24
Treated yaws	—	2	2
Family history of syphilis	29	4	33
Gonorrhoea lymphogranuloma chancroid—early and treated	1 532	14	1 546
Non gonococcal urethritis balanitis—early and treated	2 515	20	2 535
Previous unexpected positive serology	186	87	273
Abortion and stillbirth	36	1	37
Epididymitis orchitis prostatitis	138	1	139
Skin diseases	321	2	323
Vascular disease	129	7	136
Orthopaedic cases	211	5	216
Ophthalmic cases	131	8	139
Ear nose and throat cases	154	4	158
Lymphadenopathy	64	4	68
Miscellaneous cases	482	8	490
Total	15 284	716	16 000

The routine examinations include such cases as fitness medicals phobias etc Genital lesions include a number of conditions ranging from minor traumatic lesions to warts The miscellaneous cases are predominantly from the general medical wards

Kingdom or Western Europe The origins of the specimens according to the diagnoses accompanying the sera are shown in Table I, in which certain points need emphasis First, the diagnoses are provisional and in some cases were changed later, the diagnoses in Table I and subsequent Tables do not, therefore, show absolute correlation Secondly, the Table is an analysis of sera and not of cases A large number of the specimens arise as a result of many tests being undertaken on the same patient, and Table I, therefore, gives no indication of the incidence of venereal disease in the Royal Air Force Thirdly, the tendency to repeat tests of doubtful interpretation more frequently than those in which the serological and clinical diagnoses are mutually confirmatory exaggerates the incidence of biological false positive tests Finally, the apparent, but fallacious, high incidence of positive tests obtained from blood donors arises because a large number of these specimens were selected as positive at laboratories of the National Blood Transfusion Service, particularly those concerned with the recruit centres mentioned later

RESULTS

Of the 16,000 sera tested, 15,284 (95 53 per cent) were non-reactive, while 716 (4 47 per cent) were reactive with one or more of the tests used The results are given in detail in Table II, which shows that all three reactions agreed in supporting the diagnosis of syphilis in 2 49 per cent of specimens There was thus full agreement between the three reactions in 98 02 per cent of tests, which is rather greater than that obtained by Price (1948) and compares favourably with the results of Osmond (1950) contrasting the Wassermann and Kahn reactions

There was disagreement in 317 tests (1 98 per cent of the whole), the PPR agreed with the Kahn in 77 tests and with the WR in 120 tests In the remaining 120 tests, the Wassermann and Kahn reactions agreed to the exclusion of the PPR

The reactions in seventeen cases of early syphilis are analysed in Table III All these cases were untreated primary syphilis except one (Case C525

TABLE III
REACTIONS OBTAINED FROM SEVENTEEN CASES OF ACUTE SYPHILIS

Reaction	Kahn	+	−	−	−	Total
	PPR	+	−	−	−	
	Wassermann	−	−	+	−	
Test	First diagnostic	10	4	2	1	17
	Second confirmatory	11	1	—	—	12

TABLE II
ANALYSIS OF 716 POSITIVELY REACTING SERA FROM 16 000 TESTS

Reaction									Total	Tests in Series (per cent)
	Kahn	−	−	−	−	−	−	−		
	PPR	+	−	−	−	−	−	−		
	Wassermann	−	−	−	−	−	−	−		
Diagnostic Sera	True syphilis	123 (59)	1 (1)	—	9 (5)	—	—	2 (2)	135	0 84
	False positive	5 (5)	84 (80)	3 (3)	30 (20)	1 (1)	4 (3)	32 (22)	159	0 99
	Untraceable	—	1 (1)	2 (2)	—	1 (1)	—	3 (3)	7	0 04
Treated Syphilis		271 (81)	26 (21)	4 (3)	76 (39)	6 (6)	1 (1)	31 (23)	415	2 59
Total		399	112	9	115	8	5	68	716	4 47
Overall Incidence (per cent)		2 49	0 7	0·06	0 72	0 05	0 03	0·42		
Incidence in Positive Tests (per cent)		55 7	15 6	1 2	16 2	1 1	0 7	9 5		

The figures in parentheses indicate the number of patients from whom the sera were obtained

in Appendix) One case was negative to all three reactions at first test, of the remainder, the Kahn was positive fourteen times, the PPR ten times, and the Wassermann sixteen times Of the cases tested a second time before treatment was begun, only one failed to respond to all three reactions, and it seems that the diagnosis was open to doubt

In Fig 1 the titres obtained by the PPR and Wassermann techniques on identical specimens of serum are compared All cases where a comparison was possible are included, but pre-treatment cases have been demarcated from the rest Similar figures for the Kahn reaction cannot be produced because it was not performed quantitatively

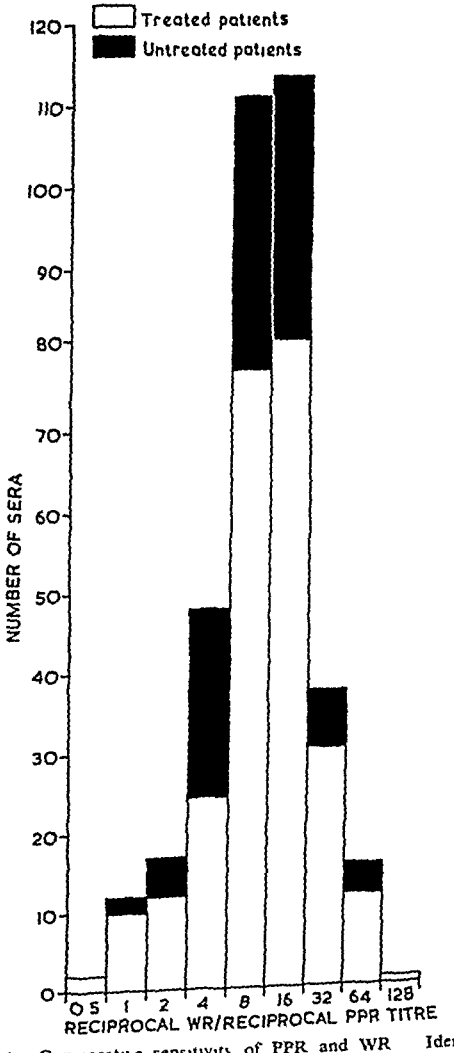

FIG 1.—Comparative sensitivity of PPR and WR Identical specimens of serum from treated and untreated syphilitics have been titrated by both techniques the titres obtained having been expressed as a ratio

The effect of treatment in each of the reactions in the test battery is shown in Table IV and diagrammatically in Fig 2 Sera are included in which one or more reactions were positive, and the results are related to the time following treatment The total number of tests in which there was sufficient information for inclusion in the Table was 330, and in many cases the period of observation has been rather short Where the total number of tests performed at a given time was less than ten, the points have not been plotted in Fig 2

The number of times each reaction, if used alone or in conjunction with another one, would have failed to demonstrate a treated syphilitic who was still reactive, is shown in Table V (opposite) From this it will be seen that the PPR if used alone would have failed to pick up such a case in 32 per cent of the tests as opposed to 9 1 per cent for the Kahn and 7 5 per cent for the WR A combination of the

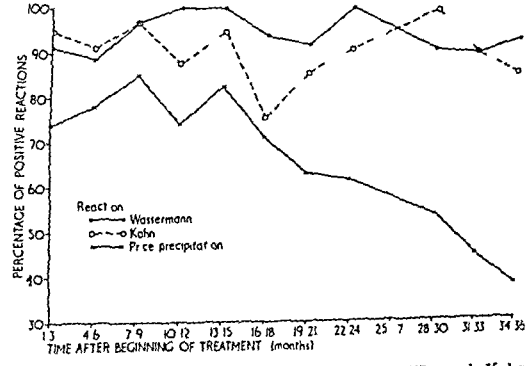

FIG 2.—Response to treatment of the PPR WR and Kahn *Treated cases still* showing reactivity to one or more tests have been collected in groups according to the time following treatment The number of positive reactions given by each test is expressed as a percentage of the group *Wholly negative* sera are not included

TABLE IV

POSITIVE REACTIONS OBTAINED WITH THE THREE REACTIONS RELATED TO TIME AFTER TREATMENT OF PROVEN SYPHILIS

Time after Treatment (mths)	Total Positive by One or More Reactions	Reaction		
		Kahn +	PPR +	Wassermann +
1– 3	52	50	39	48
4– 6	65	59	51	58
7– 9	39	38	33	38
10–12	32	28	24	32
13–15	23	22	19	23
16–18	21	16	15	20
19–21	16	14	10	15
22–24	13	12	8	13
25–27	9	8	7	9
28–30	13	13	7	12
31–33	11	10	5	10
34–36	16	14	6	15
37–39	9	8	5	8
40–42	5	4	2	4
43–45	2	1	0	2
46–48	1	0	1	1
49–51	3	3	2	3

TABLE V

REAGIN CONTAINING SERA FROM TREATED SYPHILIS
RELATIVE SENSITIVITIES OF THE THREE REACTIONS

Reaction	Results		Per cent Non-reactors
	Positive	Negative	
Total	415	—	—
Kahn	377	38	9 1
PPR	282	133	32 0
Wassermann	384	31	7 5
Kahn+PPR	384	31	7 5
Wassermann+PPR	389	26	6 3
Kahn+Wassermann	414	1	0 2

PPR and Kahn would have missed 7 5 per cent, the PPR and the WR 6 3 per cent, while the WR and Kahn combined would have failed in only 0 2 per cent

In positive tests regarded as false, the PPR was positive thirteen times, the WR 68, and the Kahn 122 times A positive result has been assessed as false if it was never reproducible in the untreated patient (technical false positive) or if the serum reaction showed steady reversion to negative on serial testing in the absence of treatment (biologic false positive) Occasional sera which have not reverted to normal have been classified as biologic false positive on a purely clinical basis The results in the 159 false positive diagnostic tests are further

TABLE VI

INCIDENCE OF FALSE POSITIVE TESTS IN THE SERIES AND RELATIVE SPECIFICITIES OF THE THREE REACTIONS

Incidence of False Positive Results		Overall (per cent)	In Positive Tests (per cent)	In Positive Diagnostic Tests (per cent)
Sero positivity judged by	One test only positive	1 0	22 4	54 1
	Flocculation and complement fixation tests both positive	0 23	5 1	12 3
	All three reactions positive	0 03	0 7	1 7
Incidence of false positive tests given by individual reactions	Kahn	0 76	17 2	41 5
	PPR	0 08	1 8	4 4
	Wassermann	0 43	9 7	23 1

elaborated in Table VI The overall incidence of false positive serology was almost exactly 1 per cent, which is higher than would be anticipated (Wolman, 1946, Stokes and James, 1949, Price, 1954) More than half the false positive tests arose as a result of an isolated false positive Kahn reaction —a finding which is so common (Bossak and others, 1953, Fischer, 1950, Levitan and others, 1952) that a diagnosis of syphilis on such grounds would be unthinkable If a positive flocculation test together with a positive complement-fixation test is taken as the minimum finding compatible with the serological diagnosis of syphilis (Beelar, Zimmerman and Manchester, 1949, Colquhoun, 1950), the overall incidence of false positive serology is reduced to 0 23 per cent, and the percentage of positive diagnostic tests ultimately considered false is reduced from 54 1 per cent for a single test to 12 3 per cent If full agreement of all three tests were to be taken as the criterion for the sero-diagnosis of syphilis, an incidence of a false positive diagnosis of syphilis in 1 7 per cent of positive diagnostic tests would arise This rigid principle would also involve the failure to diagnose syphilis in 8 8 per cent of sera from untreated cases

It is impossible from our records to estimate the number of times all three reactions were falsely negative together

DISCUSSION

Sensitivity of the Reactions

There are various ways in which the sensitivity of the PPR can be compared with the sensitivity of the other tests

First, an analysis of very early cases of syphilis can be made and the order in which the reactions normally became positive can be assessed Table III, which shows the results in such patients, offers some evidence that, of the three reactions under consideration, the PPR is the least sensitive in early syphilis, failing to identify seven out of seventeen cases Price's results in 1948 showed that the Kahn was superior to the PPR in this respect, but at this time the Wassermann was not attuned to such a degree of sensitivity It is interesting to note that, using Price's modification of the Wassermann reaction (Price, 1950), only one case of early syphilis, which was negative to all three reactions, would have been missed at first test Moreover, of the seventeen cases, eight showed a Wassermann titre of 1 128 or higher before treatment began

Secondly, the relative sensitivity of the tests under consideration could be judged by comparing the titres obtained on identical specimens of serum from known cases of syphilis Fig 1 shows that, when pre-treatment cases only are considered, the PPR was never more sensitive than the WR and that in the majority of cases the WR was four to sixteen times more sensitive than the PPR, a finding which coincides with that of Price (1949a) When all sera showing a positive Wassermann and PPP, including those from treated cases, are considered, it will be seen that the pattern of results is not materially altered though the superior sensitivity of the Wassermann reaction is, perhaps, rather more accentuated

Thirdly, the sensitivity may be compared by following the effect of treatment on each reaction The results in Table IV and the comparative slopes of the graph in Fig 2 show clearly that there is a tendency for the PPR to revert to normal before the Wassermann and the Kahn The final evidence as to the relative sensitivity of the three reactions is contained in Table V The results give a definite impression that the PPR is markedly less sensitive than either the Kahn or the Wassermann reaction In both these cases the assessment of sensitivity is based on the assumption that persistence of one positive serological reaction indicates incomplete surveillance—a highly suspect belief (Heywood, 1952, Redmond, Nicol, and Shooter, 1952, Cannefax and Johnwick, 1954) It is possible that a careful clinico-serological survey might find that the apparent insensitivity of the PPR was a definite advantage in assessing the results of treatment

Until further information is available, however, it is clear that the PPR is insufficiently sensitive for use as a screening test and should never be used as a single reaction for the exclusion of syphilis

Specificity of the Reactions

The specificity of a reaction can be judged only by the number of false positive results it gives Before considering the individual reactions it seems necessary to investigate the causes of the rather high general incidence of false positive tests in our series

One possibility is that the general laboratory technique is at fault Such an explanation could be tenable so far as the isolated positive Kahn test is concerned If these tests are divided into those before 1954 and those in 1954 and onwards it is found that the incidence of the isolated false positive Kahn before 1954 was 0 64 per cent while from 1954 onwards it was 0 43 per cent Of the 1954 cases, 71 per cent were in the first half of the year, while this false positive reaction has not been seen in the early part of 1955 covered by this series We believe this decline to be associated with the gradual introduction of prepared merthiolate bottles in January, 1954 The Kahn reaction appears to be hypersensitive to the effects of travel (Sautet, 1951), such effects being largely beyond the control of the laboratory although merthiolate seems to improve the position (Rein and Kelcec, 1954)

Even so, the incidence of positive Kahn tests is higher than we should like, and for further relevant information we are indebted to Knox (1955), who collected information from 4,800 volunteer blood donors from healthy recruits to the Royal Air Force and found that 104 (2 2 per cent) were rejected by the Transfusion Service as a result of a positive Kahn being obtained During the period January to June, 1954, another recruit centre, largely Women's Royal Air Force, had 34 similar rejections, and a third, the largest of the three, 73 In the last two cases the percentage of rejection is not available It would, therefore, seem that false positive serology is a general finding in groups comparable to ours and not an isolated occurrence in one laboratory

The combination of false positive Kahn and Wassermann reactions has occurred in 0 22 per cent of tests in our series, a frequency which constitutes a serious problem because a patient giving such a result stands in grave danger of being diagnosed as syphilitic This reaction was also obtained in eleven blood donors from the Women's Royal Air Force centre and in nineteen donors from the largest recruit centre, but, again, the incidence is not available It is interesting to note that Price (1948) did not obtain such a result in his series

We are convinced that, while many of the results which show a positive Kahn only can be ascribed to postal or storage effects, the combination of false positive Kahn and Wassermann reactions is a definite biological entity which is curiously prevalent in our series and in the comparable groups reported by Knox (1955) We believe that this is due to the high state of active immunization effected in the Armed Forces Many authors (Davis, 1944, Rein and Elsberg, 1945, Perrot, 1948, Stokes and James, 1949, Mahoney and Zwally, 1949, Kay and Rice, 1951, Archambault, 1951, Price, 1954) agree that this may be a potent cause of false positive reactions for syphilis, though Rosenthal and Widelock (1948) think the risk to be exaggerated In our present series the results are not particularly helpful because of lack of relevant histories Some suggestive evidence can, however, be gained from the 4,800 blood donors mentioned above All these persons had been vaccinated against smallpox shortly before the test, the average being 4 weeks On the other hand, almost exactly 50 per cent of the 104 positives had deliberately been excluded from the routine TABT immunization offered to R A F recruits, TABT inoculation might, therefore, be excluded as a cause of false positive syphilitic serology Subsequently, Knox arranged for a group of blood donor volunteers to be tested before vaccination 980 tests were made and the incidence of false positive serology was reported as nil There is thus some evidence that vaccination against smallpox may give up to 2 per cent of false positive results, a situation which is of the utmost importance in groups such as the Armed Forces and particularly where a sensitive Wassermann

technique is in use Many of the false positive tests previously reported from this laboratory (Roberts and Swale, 1949) probably fall into this group

The second most frequent pattern of false positive tests was that which showed a positive complement-fixation test only In view of the generally accepted superiority of the complement-fixation test as regards specificity (Fischer, 1950, Bossak and others, 1953, Pecora, 1953), this is an important group In four cases (five tests) the positive Wassermann reaction was the final stage in a steady gradation from a combined false Kahn and false Wassermann, the Wassermann persisting longer (Case G231 in the Appendix is a typical example)

In eighteen cases (27 tests) the Wassermann was the only one of the three reactions in use ever to be positive—one particularly interesting case was B35 in the Appendix Three of these tests on sera from three healthy babies born to syphilitic mothers who were under treatment were due to a carry-over of maternal reagin (Bundesen and Aron, 1950, Denecke, 1951) It is important to note that Price's modification of the Wassermann reaction may produce false positive results without similar flocculation results in up to 10 per cent of the total positive sera submitted for diagnosis

The small group of five patients in which all three reactions were falsely positive is most important Two of these false positives almost certainly arose as a result of clerical error and substitution of specimens One was a very weak reaction throughout and the other two were definite positives and were only proved to be biologic false positives by careful follow-up Both the latter had recently been vaccinated against smallpox

The remaining eight false positive tests consist of four tests (three patients) in which the PPR was positive in low titre when both Wassermann and Kahn were negative, three in which the flocculation tests were weakly positive in the presence of a negative complement-fixation test, and one where the Kahn was the only negative reaction of the three Apart from the five cases in which all the reactions were positive, these eight tests represent the only failures of the PPR in the series in regard to specificity

The specificity of the PPR (Table VI) is quite remarkable, and we have increasingly come to regard the PPR as the most useful reaction in the evaluation of a positive diagnostic test A positive PPR appears to be the best 'standard' serological evidence of active syphilitic infection available If the Wassermann reaction is also positive, the case for diagnosing syphilis is extremely good providing steps are taken to exclude clerical error In such circumstances, only 1 4 per cent of positive diagnostic tests would eventually prove to be false and some of these should be anticipated by the generally low titre of the PPR (Case C19 in Appendix) Another great value of the PPR is demonstrated by the fact that, of 33 sera from non-syphilitic persons giving a positive Kahn and Wassermann test of sufficient clarity to warrant a tentative diagnosis of syphilis, the PPR indicated the incorrectness of the result in all but three The value of the PPR is, however, limited when no clinical history is available, as a negative reaction can well occur in early untreated or late treated syphilis

It may be argued that the specificity of the PPR is merely a reflection of its diminished sensitivity This may be true in part, but we do not think it the whole explanation In the first place the combination "Wassermann −, Kahn +, PPR −" occurs as a false positive so frequently that it is hard to avoid attributing the negative PPR to specificity Secondly, several of our false positive cases have had WR titres in excess of 1 128 together with a negative PPR Such a discrepancy is hardly explicable purely on the basis of relative sensitivity Finally, it seems unlikely that the great excess of "Wassermann −, Kahn +, PPR −" reactions over "Wassermann −, Kahn +, PPR +" can be put down solely to a difference in sensitivity

PRACTICAL APPLICATION

No serological test could be simpler to perform than the PPR The antigen is easy to prepare and is stable under a wide range of temperature conditions (Macfarlane, Anderson, and Pinion, 1953, Evans, 1954) We have, however, found that a very fine flocculation is invariably present in the negative controls and, for this reason, we strongly advocate reading the PPR before other flocculation tests, the reverse will lead to prejudiced reading of the PPR

The very high degree of specificity of the PPR found in this series suggests that it is a reaction which could with advantage be used as a routine To use the reaction by itself as a screening test, say of blood donors is strongly contraindicated, since a high percentage of incompletely followed cases of syphilis will be missed For use in any sphere, the PPR must be combined with one or more reactions of superior sensitivity

Probably the commonest combination of tests in use in Great Britain is that of the Wassermann and Kahn reactions We find that both these reactions have very much the same sensitivity The Wassermann reaction appears to be the rather more specific

but the routine use of merthiolate may remove this apparent advantage There is a tendency for a biologic false positive Wassermann to persist longer than a similar Kahn reaction, and in treated cases of late syphilis the Wassermann takes rather longer to reach normal than the Kahn , in early syphilis the reverse tends to occur All in all, there seems little to choose between the reactions and it might be possible to substitute one or the other by the PPR and thus to improve the test battery without complicating it

The combination of the Wassermann and PPR without the Kahn would result in the elimination of over 50 per cent of the false positive results in the present series On the other hand, one early case of syphilis would have been missed and 6 3 per cent of reagin-containing sera from treated syphilitics would have been reported as sero-negative, though whether this would be a disadvantage, in view of the highly non-specific nature of the isolated positive Kahn, is at least arguable It would seem that the Kahn reaction could be eliminated without loss of efficiency However, the Price modification of the Wassermann reaction is not easy to carry out, and it is desirable to have a highly sensitive flocculation test on hand as a check on possible technical false positive complement-fixation tests To carry out the Kahn test in parallel with the PPR involves very little extra work and, on the whole, we would advocate its retention

If the Wassermann reaction could be discarded, much time and effort would be saved In this series, such a practice would have resulted in two cases of early syphilis being missed and 7 5 per cent of treated syphilitic reagin-containing sera being classed as negative Twenty per cent of false positive reactions would have been eliminated Thus, for a small laboratory with a shortage of skilled technicians, a test battery of Kahn and PPR would give results of reasonable efficiency Whenever possible, however, we would advocate the inclusion of the Wassermann in the test reactions It has historic merit and is the test invariably requested by clinicians , it involves a technique wholly different from that required for flocculation tests, which, combined with the fact that it is usually performed on a different day, tends to eliminate false positive results due to laboratory error , finally, only the inclusion of a complement-fixation test can be expected to eliminate the prozone exhibited by some strongly reactive sera (Beelar and others, 1949)

In tropical conditions, where the WR is notoriously fickle and the reagents hard to keep, the Kahn and PPR used alone might prove to be the best test battery available In normal circumstances however, we feel that the PPR, valuable test though it is, cannot completely replace the Kahn or Wassermann reactions The performance of the Wassermann, Kahn, and Price reactions in parallel appears to be a highly effective and relatively simple method of diagnosing or eliminating syphilis

SUMMARY

The results of submitting 16,000 consecutive sera to test by the Kahn, Wassermann, and Price Precipitation reactions are presented, and the usefulness of the PPR is compared with that of the other two tests

The PPR is shown to be more specific than either of the other reactions, but is less sensitive as measured by the effect of treatment on the serum reactions

The incidence of false positive tests for syphilis in the series is discussed and a possible reason for the high incidence elaborated

The constitution of a simple test battery is discussed It is considered that a combination of Kahn, PPR, and Wassermann is nearly ideal In circumstances where the carrying out of the Wassermann is contraindicated, a combination of the Kahn test and the PPR will give reasonably accurate results

We are indebted to our fellow officers and technicians who have given us all possible help throughout this investigation We should particularly like to thank the officers in charge of several hospital laboratories who have gone to much trouble to trace patients' records for us In this respect our especial thanks are due to Squadron Leaders A N Kingon and C S Pitcher the officers in charge of the Special Treatment Centres in the United Kingdom and Western Europe respectively Our thanks are also due to the Director General of Medical Services Roval Air Force who has kindly given us permission to publish this paper

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APPENDIX

Case Reports

Case B35 —A young airman traumatized his genitalia, and 10 days later was found to have a Wassermann reaction of titre 1 64 with negative Kahn and PPR One month later the Wassermann reaction titre was was 1 128 Monthly tests for the next 4 months showed a Wassermann reaction titre ranging between 1 64 and 1 128 , at no time was the Kahn or PPR positive He was not seen again until 2 years after the original test when he was found to have a Wassermann reaction of 1 64 It is considered that this case is an example of the rare naturally occurring "biologic false positive" The case illustrates that not all biologic false positives will revert to negative in a short time (Paillard and Bolay, 1951) Since this paper was submitted for publication, this airman has been shown to have a negative treponemal immobilization test

Case B86 —This case, of frank early primary syphilis, shows the characteristic pattern of tests in acute cases At the first test the results were Kahn + , PPR, 1 32 , Wassermann 1 32 , re-tested 10 days later to exclude clerical error, the results were Kahn + , PPR, 1 64 , Wassermann, 1 128 + , 6 weeks after treatment was begun the PPR was negative and remained so The Wassermann was 1 16 at 6 weeks 1 4 at 10 and 14 weeks, and negative at 18 weeks The Kahn was positive until the 18th week All reactions were negative by the 24th week

Case C19 —This patient was referred through the ophthalmic department as a case of iritis The following results were found Kahn + , PPR, 1 2 , Wassermann 1 64 It was remarked that he had recently been vaccinated but infectious mononucleosis was not excluded Ten days later the PPR was negative, Kahn — Wassermann 1 16 A fortnight later all tests were negative and remained so No treatment which could have affected his serology was ever given The low titre of the PPR was commented upon at the time as possibly indicating a false positive

Case C525 —An airman had a typical history and signs of a non specific urethritis appearing 10 days after exposure He was treated with aureomycin while his serology was being investigated, but treatment was stopped when his results were found to be Kahn + , PPR— , Wassermann, 1 8 On recall he stated that the day after examination he had developed a lump in the pipe " which disappeared rapidly His PPR was now positive at 1 1 and his Wassermann 1 16 , 14 weeks after the original test all three reactions were again positive, and by 18 weeks the PPR titre was rising (1 4) He was then treated as a case of intraurethral chancre The serology is interesting as it would seem that the course of aureomycin inhibited the emergence of a positive PPR

Case G19 —This case was clinically diagnosed as late secondary syphilis Pre-treatment tests showed Kahn + , PPR, 1 8 , Wassermann, 1 64 One month after treatment the PPR had fallen to 1 2 and the Wassermann to 1 16 At 2, 3, and 4 months the PPR was negative, the Kahn positive, and the Wassermann ranged between 1 4 and 1 8 At 6 months all tests were negative but at 10 months the Wassermann was positive alone at 1 8, and again at 12 months the Kahn and PPR were negative, the Wassermann being 1 4 All reactions were negative at 13 months and have remained so This case illustrates the tendency for the Wassermann to remain positive the longest of the three reactions in the more chronic cases (see Case B86)

Case G231 —A recruit blood donor volunteer gave the following serological results Kahn —, PPR — Wassermann, 1 128— 3 weeks later the results were similar, save that the Wassermann titre was now 1 32 After a further month the Kahn was negative and the Wassermann 1 4 , 3 months after the original test all reactions were negative and they have since remained so No treatment was given The interesting points are first the negative PPR firmly suggesting a false positive secondly the very high titre of the Wassermann associated with a negative PPR thirdly, the tendency for the Wassermann reaction to persist rather longer than the Kahn when both are biologically falsely positive

Brit J venet Dis (1955), **31**, 262

A NOTE ON THE ESTABLISHMENT AND MAINTENANCE OF THE NICHOLS STRAIN OF VIRULENT *T PALLIDUM* IN RABBITS IN WARM COUNTRIES*

BY

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The Nichols strain of virulent *T pallidum*, isolated and maintained by serial transmission in live rabbit testes, is being used as the source of specific antigen in the Treponemal Immobilization (TPI) and Treponemal Agglutination (TPA) tests for syphilis It has been stressed by investigators in this field that the rabbits, after inoculation with the treponemata, should be kept in air-conditioned (18 to 20°C) rooms to produce lesions within a comparatively short incubation period and thereby make available suitable specific antigen Treponemes apparently prefer a cool environment and cool tissues to multiply and thrive well It has been possible on actual trial, however, to produce infection by the intratesticular route in rabbits kept in the natural warm (24 6 to 33 4°C) animal room conditions at Madras, India, within an incubation period of about 10 days comparable with that obtained in a cool or air-conditioned environment The Nichols strain has been maintained successfully by serial transmission in rabbit testes at regular intervals of about 10 days, throughout the last 12 months

Material and Methods

The Nichols strain of *T pallidum* was obtained by air mail from the State Serum Institute, Copenhagen It arrived in Madras about 72 hrs after dispatch as frozen rabbit testes syphilomata, kept frozen in thick-walled, large, glass test-tubes, packed in solid carbon-dioxide in a thermos vacuum jar

Immediately on arrival, the testes were rapidly thawed in running cold water, and cut into thin slices with a pair of sharp scissors A pestle and mortar was used to grind them into an emulsion with a little fine sand and about 5 ml per testis of 25 per cent normal rabbit serum in saline The emulsion was then lightly centrifuged at 1,500 revolutions per minute for 7 min to sediment the gross particles of tissue and sand A drop of supernatant fluid showed thirty to forty actively motile treponemes per field of the dark-field microscope, with the high-dry objective, corresponding to 30 to 40 million treponemes per ml of the suspension With a tuberculin syringe and a 24-gauge 1-in needle, 0 75 ml of the suspension was inoculated in equal halves through each of the two poles of each testis of young adult rabbits of mixed breed The rabbits were kept in individual cages in the animal room (not air-conditioned), and were observed daily by palpation of the testes for signs of infection By the eighth to ninth day, diffusely indurated syphilomata of the testes were found, and specific infection was confirmed by dark-field examination of testicular fluid drawn by syringe and needle puncture for live treponemes Within 24 hrs the rabbits were killed by air embolism into the ear vein The scrotum was clamped and cut off The testes were enucleated, sliced, and ground into an emulsion as before, with 5 ml of 25 per cent normal rabbit serum in saline per testis, so that the centrifuged suspension contained thirty to forty treponemes per dark field This was passaged intratesticularly, as before, into the next series of rabbits All these procedures were carried out as quickly as possible under aseptic conditions, with surgical gloves

Results

The Nichols strain of *T pallidum* was received during February, 1954, and by February, 1955, 122 rabbits in 35 series (average three rabbits) were used During this period the average mean minimum and maximum temperatures noted in Madras were 24 7 and 33 4°C respectively The mean incubation period of infection, as calculated by finding the mean of averages for every passage, was 10 76 days (standard deviation ±2 27) At the height of summer in Madras, namely, during April, May, and June, the average mean minimum and maximum temperatures were 27 8 and 37° C respectively, when the corresponding average mean incubation period was 11 05 days (standard deviation ±2 25) The difference in the incubation periods is not considered significant ($t = 0\ 2$, $P = 0\ 563$) Several batches of a stable specifically agglutinable antigen suspension were prepared from these treponemes for treponemal agglutination tests for syphilis

* Received for publication July 19, 1955

Discussion

Rich, Chesney, and Turner (1933) and Cumberland and Turner (1949), working with experimental rabbit syphilis, suggested that the production of a clinical lesion in syphilis is the end-result of a logarithmic multiplication of treponemes in the inoculum The treponemes have little resistance to high temperatures, the rate of multiplication is slower, and more time is required for the accumulation of sufficient organisms to produce a clinical lesion in syphilis in a warm environment Hollander and Turner (1954) in their experiments with the incubation period and early development of syphilitic lesions in rabbits, found that environmental temperature had an important influence on the course of experimental treponemal infection, and that this influence was exerted through its effect on the local temperature of tissues This was particularly noticed when rabbits were infected intradermally on the back The dark-field positive primary lesions invariably appeared within significantly longer incubation periods when the rabbits were maintained in natural warm conditions of 29 to 35° C as compared with rabbits kept in natural cool conditions in the winter months and/or in air-conditioned rooms at 18 to 20° C However, in one similar experiment, no significant difference was noted between the incubation period of infections producing testicular syphilomata in a warm environment and that in a cool environment Moore and Quick (1924) found that the temperature of the mammalian testis is normally maintained at a level considerably below the abdominal temperature, the muscles of the scrotum apparently controlling it by the elevation or lowering of the testes as required Obviously, the testes in rabbits may be able to maintain a relatively constant optimum temperature for normal multiplication of treponemes in warm and cool surroundings These findings seem to have been confirmed by us by the successful intratesticular infection of rabbits with an average incubation period of about 10 days, and maintenance by serial passage during 12 months at intervals of about 10 days The incubation period of infection, the type of syphilitic orchitis produced, and the number of treponemes, suitable for preparing specific antigen, obtained from the testes of infected Madras rabbits, compare well with those seen by the senior author (C W C) in the U S A in rabbits kept in air-conditioned rooms, and also with those obtained by him in his similar experiments under natural cool conditions in London However, it is stressed that in these circumstances the number of treponemes in the infective inoculum is very important and that a sufficient density of at least 30 to 40 million per ml must be inoculated into the testes to obtain satisfactory results

Conclusion

It is concluded that, to isolate and maintain the virulent strain of *T pallidum* for preparing suitable specific antigen for tests for syphilis, and for studying experimental syphilis and the biology of the virulent treponemes, it may not be necessary to maintain rabbits in air-conditioned animal rooms in tropical warm countries provided they are inoculated intratesticularly with an adequately infective inoculum

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BOOK REVIEWS

Common Skin Diseases By A C Roxburgh 10th ed, 1955 Pp xxxii + 516, 8 col pl, 215 illus H K Lewis, London (30s)

This is the tenth edition of "Common Skin Diseases" since it was first published over 20 years ago What better testimony could there be to the well-deserved popularity of this work among both students and practitioners This edition includes an admirable summing-up of the essentials of most of the advances of recent years in technique and treatment, and yet the book has not become unwieldy Dr Roxburgh was an expert in the art of sifting the wheat from the chaff and the result is a really practical and concise handbook Most useful sections are added on the uses in dermatology of ACTH and cortisone, the more recent antibiotics, and particularly on the recent work on the lupus erythematosus phenomenon and lupus erythematosus cells The use of Isoniazid in lupus vulgaris, Mepacrine in lupus erythematosus, and Ammi Majus derivations in vitiligo are the subjects of additional brief paragraphs

The section devoted to venereology is of necessity brief and not intended to be comprehensive The cutaneous manifestations of syphilis are particularly well dealt with and, both here and, indeed, throughout the whole book the illustrations are excellent The statement that 90 per cent of genital sores (where the question of syphilis may arise) are syphilitic, is now misleading, at least in Britain Chancroid indeed is a rarity, but the common genital sores of septic herpes and the septic subpreputial erosions in balanoposthitis are omitted A brief account of dark-ground technique in diagnosis could usefully be included

This book harvests the fruits of a lifetime's personal experience and the death of Dr A C Roxburgh, following so soon after his personal revision of this edition, leaves a gap which will indeed be difficult to fill A J G

Diseases of the Mouth (Dermatologie der Mundhohle und der Mundumgebung) By A Greither, with a foreword by Prof W Schonfeld 1955 Pp 262 191 illus Georg Thieme, Stuttgart (DM 39 60)

The short English title has been chosen because it seems impossible to translate literally the title of this book which, being intended for the use of the dermatologist the physician, the ear-nose-throat surgeon and the dental surgeon, deals with every conceivable condition which may occur in the mouth and on the adjacent parts of the face According to the foreword it is the first time that such a monograph has been published in German Throughout the book emphasis is laid on morphology and diagnosis, treatment is mentioned only in those sections which belong to the proper domain of the dermatologist (and venereologist) The numerous photographs are all of a very high standard, they have been taken, with a few exceptions, at the University Clinic in Heidelberg

The venereal diseases are discussed in the section which deals with the "specific infections The possibility of a gonorrhoeic infection of the mouth is rejected, but the possibility—albeit an extremely rare one—of the occurrence of an ulcus molle or a granuloma inguinale on the tongue or on the lips is admitted Lympho granuloma inguinale can cause, also very rarely, a stomatitis or an angina* The syphilitic lesions are described in detail and are extremely well illustrated but the lesions caused by other treponematoses are only briefly mentioned The large number of references contributes greatly to the usefulness of the book

A F

* Malfatti, G (1948) *Oto rino laring ital* 17 63

A History of Dermatology in Philadelphia By Reuben Friedman 1955 Pp 556, 137 illus Froben Press Inc Florida ($10)

This book falls naturally into three periods up to 1870, when Louis A Duhring started consultant practice after 2 years of post-graduate study in Europe, the Duhring period 1870 to 1910, and the period after Duhring The pioneer work of Duhring and Shoemaker has been ably maintained and expanded by successive groups of brilliant dermatological disciples of the old masters, and for many years the reputation of Philadelphia particularly as a centre for dermatological research and post graduate training has been a proud one The present book by Dr Friedman is unusual but interesting It is part biography and part an historical record being illustrated not only by photographs of dermatologists but by facsimile reproductions of documents and extracts of historic interest Dermatologists in Britain should enjoy the whole book while venereologists will find the period of John H Stokes 1924 onwards particularly informative S M L

BACK NUMBERS OF THE *BRITISH JOURNAL OF VENEREAL DISEASES*

If any readers would be willing to dispose of copies of early issues of the *British Journal of Venereal Diseases* particularly volumes 1 to 19 would they please communicate with the Publishing Manager B M A House Tavistock Square, London, W C 1

ABSTRACTS

This section of the JOURNAL *is published in collaboration with the two abstracting Journals,* ABSTRACTS OF WORLD MEDICINE *and* OPHTHALMIC LITERATURE, *published by the British Medical Association The abstracts are divided into the following sections Syphilis (Clinical, Therapy, Serology, Pathology, Experimental), Gonorrhoea, Non-Gonococcal Urethritis and Allied Conditions, Chemotherapy, Public Health and Social Aspects, Miscellaneous After each subsection of abstracts follows a list of articles that have been noted but not abstracted All subsections will not necessarily be represented in each issue*

SYPHILIS (Clinical)

Follow-up Studies in Cardiovascular Syphilis KALZ, F, and SCOTT, A I (1955) *Canad med Ass J*, 72, 274 5 refs

The authors, believing that ' detailed studies of the life expectancy and the general prognosis of adequately treated patients should be of practical value ', report their findings in 111 cases of cardiovascular syphilis treated before 1948 and followed up at the Royal Victoria Hospital, Montreal Only two cases were lost to observation, 84 were observed for at least 5 years, 53 for 10 years, and 25 for 15 years Altogether there were 46 deaths, by no means all attributable to syphilis The frequency and causes of death are tabulated and discussed The authors consider the following classification of cases of cardiovascular syphilis to be useful

(1) Uncomplicated aortitis,
(2) Aortitis complicated by simple aortic insufficiency but without signs of coronary disease or congestive failure,
(3) Aortitis complicated by coronary involvement (with or without aortic insufficiency),
(4) Cardiovascular syphilis, with congestive failure,
(5) Saccular aneurysm

They find that with appropriate treatment Groups 1 and 2 have a favourable prognosis, in Groups 3 and 4 the prognosis is unfavourable regardless of the therapy given, while that in Group 5 depends on the degree of pathological change and the state of the coronary circulation Over 30 per cent of the saccular aneurysms met with terminated in rupture The main conclusion of this study, therefore, is that prognosis depends on the presence or absence of either coronary arterial involvement or congestive failure

The authors have omitted any details of sex, race, or age distribution, since it was impossible to establish any relative correlations in this small series

Douglas J Campbell

Pre-Columbian Osseous Syphilis Skeletal Remains Found at Kinishba and Vandal Cave, Arizona, with Some Comments on Pertinent Literature COLE, H N, HARKIN, J C, KRAUS, B S, and MORITZ, A R (1955) *Arch Derm (Chicago)*, 71, 231 5 figs, 10 refs

During an examination of 57 more or less complete skeletons found in Kinishba in the White Mountains and, in one instance, in Vandal Cave, Arizona, two examples of what the authors believed to be osseous syphilis were discovered In one instance the appearances were those of diffuse gummatous osteoperiostitis of one tibia In portions of the skull from the same skeleton there was evidence of periosteal thickening, but the changes were not considered to be pathognomonic of syphilis The tibia of another skeleton showed what appeared to be the classic sabre-shin deformity of congenital syphilis Examination of roof beams in the village, or pueblo at Kinishba indicated that its 700 rooms were built in the 13th century Evidence at Vandal Cave suggested that it was inhabited at a similar time and also earlier, probably in the 7th century The authors consider these findings to indicate that syphilis was present in North America before the coming of Columbus They discuss some evidence from the literature relating to the antiquity of syphilis in America, Europe, and Asia *A J King*

Syphilis and Arteriosclerosis in Patients with Coronary Arterial Disease (Lue ed arteriosclerosi nei coronaropatici) INVERNIZZI, G (1955) *Settim med*, 43, 115 1 fig, 19 refs

Gastric Syphilis Observations on a Case of Syphilis of the Stomach Simulating a Neoplasm (Un tema di sifilide gastrica Osservazioni su di un caso clinico di sifilide neoplastiforme dello stomaco) POZZO, G, and MENEGHINI, C L (1955) *G ital Derm, Sif*, 96, 170 2 figs, 13 refs

Pulmonary Tuberculosis and Syphilis (Tuberculosis pulmonar y sifilis) SANTA-MARIA, F E, CABO REY, L A, and REY MARTINEZ, M (1955) *Med clin (Barcelona)*, 24, 178

SYPHILIS (Therapy)

Penicillin Treatment for Early Congenital Syphilis SMITH, C A, GLEESON, G A, and JENKINS, K H (1955) *Arch Pediat*, 72, 12 2 figs, 4 refs

The records of 472 cases of early congenital syphilis treated with penicillin alone during the period 1946–50 have been collected and studied at the U S Public Health Service, Washington, D C Cases in infants under 3 months of age were included only when obvious clinical signs of infection were present in addition to a positive reaction to serological testing Approximately 40 per cent of the 472 patients had been followed up for 18 to 21 months, the authors appreciate that this period is far too short to provide any information regarding the

adequacy of penicillin treatment in preventing the development of late clinical manifestations of congenital syphilis

During the follow-up period ten cases were classified as clinical or serological failures, though four of these received re-treatment on a 'clinician's decision", which on later review seems to have been unjustified Nevertheless, two patients had re-treatment for serum resistance, two for clinical relapse, and one for serological relapse In all 56 patients whose cerebrospinal fluid was examined in the post-treatment period normal results were obtained

The authors conclude that in early congenital syphilis the pattern of serological behaviour after treatment is analogous to that in the early stages of acquired disease, also that when aqueous crystalline penicillin is used best results are obtained with a dosage of 321,000 units or more per kg body weight A few of the patients were treated with penicillin in oil and beeswax with equally successful results *G L M McElligott*

Treatment of Early Syphilis Results with Penicillin G Procaine and 2 per cent Aluminium Monostearate CUTLER, J C, OLANSKY, S, and PRICE, E V (1955) *Arch Derm (Chicago)*, **71**, 239 1 fig, 5 refs

Procaine benzylpenicillin in oil with 2 per cent aluminium monostearate (PAM) has been used extensively in the treatment of syphilis, and in this paper results obtained at five treatment centres of the United States Public Health Service are reviewed, the observation period being 1 to 2 years In the sero-negative primary stage of the disease there was no obvious relationship between results and the dosage of PAM, as little as 300,000 units being effective Of the patients in this group requiring further treatment, more than 60 per cent were believed to have been re-infected, and the authors state that patients in the sero-negative primary stage are particularly liable to re-infection because they have developed the least immunity In the sero-positive primary stage little advantage was gained by increasing the total dosage beyond 2,400,000 units, the re-infection rate being 12 7 per cent with a total dosage of 1,200,000 units 23 per cent of patients required re-treatment

In the secondary stage the best results were obtained with the highest dosage used, namely 9,600,000 units, the re-infection rate being 7 per cent In one centre where dosage was computed by body weight the most satisfactory results in the secondary stage of the disease (82 per cent of cases) were obtained with the highest dosage, namely, 80 000 units per kg body weight, but the results with 40 000 units per kg were nearly as good (78 per cent) With 20,000 units per kg the percentage of successful results was 72, but with 10 000 per kg there was an abrupt fall to 44 At another centre three schemes of treatment were employed

(1) 1,200,000 units in one injection,

(2) two injections each of 1,200,000 units with 7 days interval between the injections,

(3) 4 injections each of 1,200,000 units at intervals of 7 days

The percentages of successful results were 75 1, 83 1, and 91 6 respectively At yet another centre the practice was to give a single injection of 2,400,000 units or two injections each of the same amount [with presumably 7 days' interval] Treatment was successful in 94 6 per cent and 91 8 per cent of cases respectively, indicating that no advantage was to be gained by giving two injections of this amount With 600,000 units twice a week for 8 weeks successful results were obtained in 93 8 per cent of cases

The only advantage of prolonging treatment beyond one or two injections appeared to be that the patient was in touch with the personnel of the treatment centre for a longer time, facilitating the tracing of contacts This was important from the public health point of view, and a scheme of treatment was therefore devised in which an initial injection of 2,400,000 units of PAM was followed by two injections each of 1,200,000 units at intervals of 2 to 4 days This ensured at least three visits to the clinic or, if the patient defaulted, the initial or 'insurance" dose rendered the patient non infectious and afforded an excellent chance of cure

A J King

Preliminary Report on the Effect of Carbomycin in Early Syphilis BUCKINGER, R H, HOOKINGS, C E and GARSON, W (1955) *Antibiot Med* **1**, 100 2 figs, 1 ref

A recent report (Turner and Schaeffer, *Amer J Syph*, 1954, **38**, 8, *Abstr Wld Med*, 1954, **16**, 199) having shown that carbomycin, an antibiotic derived from *Streptomyces halstedi*, was "rather effective at low serum levels in experimental syphilis in rabbits, a clinical trial of this antibiotic was undertaken at the Venereal Disease Clinic, Memphis, Tennessee

A daily dose of 2 or 3 g carbomycin was given by mouth to eleven patients with dark-field positive primary or secondary syphilis *Treponema pallidum* disappeared from the lesions in 36 to 72 hrs after the initial dose Slight side effects were observed in only two cases

[This is a preliminary report of a rather inconclusive clinical trial, but it indicates that carbomycin has some effect on *T pallidum* and that in the dosage employed it is relatively free from side-effects Longer observation of the patients and laboratory tests to determine the blood level of the antibiotic and serological results of treatment will be necessary before the value of carbomycin in the treatment of syphilis can be assessed]

Robert Lees

Treatment of Cardiovascular Syphilis (Die Behandlung der kardiovaskularen Lues) SCHEMBRA F W (1955) *Munch med Wschr*, **97**, 922 20 refs

Iodocillin" in the Treatment of Neurosyphilis (Sull uso della iodocillina nella neurolue) FLORIS V, and SEVERINI P (1955) *Minerva med (Torino)* **1**, 1317

Question of Penicillin Treatment in Neurosyphilis II Special Therapeutic Problems (La questione della terapia penicillinica nella neurolue II Problemi di terapia speciale) CALLIERI B (1955) *Clin terap (Roma)*, **8**, 253 7 figs, bibl

Treatment of Syphilis with Long Acting Penicillin (Tratamiento de la sifilis con penicilinas retardadas) GAY PRIETO, J, LOPEZ VILLAFUERTES, A, PASCUAL SANTAMERA, A, and ORUSCO HERNANDO, M (1955) *Act dermo-sifiliogr* (*Madr*), 46, 555

Treatment of Syphilis with Procaine Penicillin (Sobre el tratamiento de la sifilis por los preparados de penicilina-procaina) LOPEZ, B, and RODRIQUEZ MORALES, J (1955) *Act dermo-sifiliogr* (*Madr*), 46, 562

Cortisone and Sero-resistance (Cortisone e sieroresistenza) DEPAOLI, M, and DOGLIOTTI, M (1955) *Minerva derm* (*Torino*), 30, 89 37 refs

On the Frequency of the Jarisch-Herxheimer Reaction [In English] BLOM-IDES, C S A M, POLANO, M K, and HERRMANN, W A (1955) *Acta derm-venereol* (*Stockh*), 35, 118 4 refs

Observations on Focal Syphilis ("Island Disease") with Special Reference to the Use of Luotest, Mirion, and Kobratoxin OUTSCHOORN, A S (1954) *Ceylon med J*, 2, 238 17 refs

SYPHILIS (Serology)

Study of the TPI Test in Clinical Syphilis II Comparison with the VDRL Slide Test in Treated Early Symptomatic Syphilis EDMUNDSON, W F, KAMP, M, and OLANSKY, S (1955) *Arch Derm* (*Chicago*), 71, 384 7 refs

This report from the Venereal Disease Research Laboratory, Chamblee, Georgia, presents the results of a comparative study of the treponemal immobilization (TPI) and VDRL slide tests, which were carried out in parallel on sera from 188 patients at varying periods after adequate treatment with penicillin for early syphilis The TPI test was not performed before treatment, nor were serial tests carried out

In 77 cases the patient had been treated for primary syphilis 3 months to 4 years or more before the tests were performed Sera from only two patients (treated respectively 3 months and 1 year previously) were reactive with the VDRL test, whereas seven sera were reactive with the TPI test ("reactive" including both positive and doubtful reactions) The interval since treatment was 3 months in three of these seven cases, 1 year in one, 2 years in another, and 4 years in the remaining two cases In one case the serum was reactive with the VDRL test a year after treatment, but gave a negative TPI reaction

The tests were also carried out on sera from 111 patients who had been treated for secondary syphilis, these being reactive with the VDRL test in 33 cases and with the TPI test in 51 In about half the cases tested 3 months after treatment the serum was reactive with the TPI test, but this proportion fell to one-quarter in the cases which were not tested until 4 or more years after treatment The VDRL reaction had become negative 1 year after treatment in all but a few cases (7 4 per cent), in five of which the TPI reaction was negative

This lack of correlation between the results of the two tests emphasizes the need for careful questioning of the patient about previous antisyphilitic treatment before attempting to interpret the result of either test in this type of case *A E Wilkinson*

Study of the TPI Test in Clinical Syphilis III Late Syphilis EDMUNDSON, W F OLANSKY, S, WOOD, C E, and KAMP, M (1955) *Arch Derm* (*Chicago*), 71, 387 9 refs

A comparative study of the reactivity of sera from 120 patients with late syphilis with the quantitative Kahn test, the quantitative Kolmer test using cardiolipin antigen, the VDRL slide test, and the treponemal immobilization (TPI) test was carried out at the Venereal Disease Research Laboratory Chamblee, Georgia Both treated and untreated patients were included and the cerebrospinal fluid had been examined in all cases Symptomatic neurosyphilis of various types was present in 57 cases, asymptomatic neurosyphilis in 44, cardiovascular syphilis in fifteen and gummata in four (of the naso-oral cavity in three, of the liver in one), eighty of the patients had been treated in the past

The Kahn test gave a positive or doubtful ("reactive") result in 64 9 per cent, the Kolmer test in 85 4 per cent, the VDRL test in 78 6 per cent, and the TPI test in 98 3 per cent of the 120 patients The only two patients in whom the TPI reaction was negative were a man of 67 who had been adequately treated for early paresis in 1928 with arsphenamine and malaria, his serum having also given negative results in 1948, and a woman of 55 who had had a gumma of the palate which had been adequately treated with penicillin in 1951

The authors consider that because of its high reactivity in late syphilis, the TPI test may be helpful in the investigation of patients who have signs arousing suspicions of late syphilis which are not corroborated by the results of standard serum tests This is especially likely to occur in patients with tabes and cardiovascular syphilis *A E Wilkinson*

Test for Immobilization of *Treponema pallidum* Correlation with Some of the Standard Serologic Tests for Syphilis MACPHERSON, D J, LEDBETTER, R K, and MARTENS, V E (1955) *Amer J clin Path*, 25, 89 18 refs

Treponemal immobilization (TPI) tests were performed at the National Naval Medical Center, Bethesda, Maryland, on serum from 726 patients on whom standard tests for syphilis (STS) had given positive or doubtful results on two or more occasions and who had no clinical evidence or past history of syphilis In all cases two separate specimens of serum were examined by the TPI test [It is not stated whether there was any disagreement between the results of tests on the two specimens]

The TPI test result was positive in 437 cases and negative in 289, an incidence of 39 8 per cent non-specific STS reactions The Kahn reaction had originally been found positive in 621 cases, and 248 (39 9 per cent) were TPI-negative The Kolmer reaction was positive

in 126 cases, but the TPI reaction was negative in 27 (21 4 per cent) of these A test with cardiolipin antigen [nature not stated] had given 163 positive reactions, but serum from 48 of these patients gave a negative TPI reaction

A possible cause of non-specific STS reactions was present in only sixty of the 289 patients who were thought to have given such reactions in view of the negative TPI result These included cases of upper respiratory tract infection (eighteen), malaria (nine), infectious mononucleosis (six) pneumonia (six), virus pneumonia (four), and pregnancy (seven cases)

[These results emphasize the high proportion of cases in which no precipitating cause can be assigned for presumed non-specific STS reactions]

A E Wilkinson

Quantitative Analysis of the Sachs-Witebsky Reaction on 1,146 Sera (Analisi quantitativa di 1146 sieri con la reazione di Sachs-Witebsky) LOMUTO, G (1955) *G ital Derm Sif*, **96**, 43 Bibl

Writing from the University Skin Clinic, Bari the author points out the prognostic and therapeutic importance of a quantitative serological follow-up of syphilitic patients

In the study here described 1,146 sera from 802 patients were examined by the Sachs-Witebsky (S-W) reaction for lipoid flocculating antibody and 24 hours later the quantitative reaction of the positive sera was determined The technique used is briefly outlined The same pipette was used for all tests, and re-inactivation of the serum for the quantitative test is not necessary It was unfortunately not possible to shorten or simplify the quantitative reaction to such an extent as to render it practicable for routine application in place of the qualitative test

The most salient findings in the study were as follows Repetition of the test after 24 hrs often shows a change in titre in 17 per cent of the present cases a decrease and in 3 per cent an increase in titre occurred The level of antibody is related to the stage of syphilis and may be negative or positive at a titre of no more than one in four in primary cases, and is never below one in four in secondary cases In clinically manifest cases of tertiary syphilis it is usually lower than in secondary In untreated congenital cases the titre is usually high and a zone phenomenon often occurs , this phenomenon which the author defines as a stronger reaction at a higher dilution although this does not imply a completely negative reaction in a lower dilution, is considered to be due to excess antibody and was observed in 50 per cent of all untreated congenital cases in this series, while most other cases with zoning were of long standing

Performance of the S-W test with twice the normal amount of serum gave an attenuation of the reaction in nine cases (probably due to zoning) but an increase in intensity in 68 cases, six of these which had been negative with a normal amount of serum becoming positive the procedure is however not recommended A strongly positive complement-fixation test is usually associated with a positive S-W test result but the reverse is not true

As an example of a non specific reaction 34 out of sixty samples of serum from patients with leprosy gave positive results, many with a high titre persisting over several dilutions

The serological reactions in a number of cases were followed through a period of treatment with penicillin or with bismuth and arsphenamine The titres were inconclusive, but the author inclines to the belief that penicillin lowers the titre less than the older forms of treatment in long-standing cases In recent cases penicillin is superior *F Hillman*

Experience with the New Pallida Antigen in Syphilitic Serology (Erfahrungen mit dem neuen Pallida-Antigen in der Lues Serologie) GROPPER H (1955) *Medizinische*, No 10, 352 5 refs

The author surveys his experience at the Dermatological Clinic of the University of Tubingen in the use of the 'pallida " reaction in 3 521 cases Whereas the Wassermann reaction (WR) is dependent on the presence of a non-specific anti-lipid antibody, the pallida reaction is due to a specific antibody against spirochaetal protein A positive reaction was obtained in 641 of the 3 521 cases, and the results are compared with those of the following tests simultaneously carried out WR with cardiolipin antigen, WR with syphilitic liver, Kahn test Meinicke reaction (macroscopic and microscopic) With strongly positive sera the pallida reaction gave the highest number of positive results followed by the Meinicke reactions and Kahn test , the highest total number of positive results was given by the Meinicke reactions owing to their higher sensitivity with weakly positive sera In one clinically diagnosed case of syphilis the pallida reaction was negative whereas the other reactions were positive , on the other hand the pallida reaction alone was positive in 3 1 per cent of cases

It was found that the sensitivity of these tests was in inverse proportion to their specificity , thus the original WR and the cardiolipin WR, with relatively low sensitivity, gave more specific results than the more sensitive pallida and Meinicke reactions False positive results with the pallida reaction may be due to *lupus vulgaris* The pallida reaction tends to remain positive even in satisfactorily treated cases, unlike the cardiolipin WR and the original WR and it therefore cannot be used as a test of cure In two recent cases of syphilis followed up with all the above tests the pallida reaction was the first to become positive, followed closely by the two Meinicke reactions , owing to the early institution of treatment the ordinary WR never became positive in these cases

It is noted that Nelson s treponemal immobilization test is superior to the pallida reaction in sensitivity and specificity *F Hillman*

Specificity of the TPI (*Treponema pallidum* Immobilization) Test in the Diagnosis of Syphilis (De waarde van de treponema-pallidum immobilisatie reactie voor de diagnostiek-van syphilis) BEKKER, J H , and ONVLEE, P C (1955) *Ned T Geneesk* , 99, 1414 23 refs

Comparative Study of the Sensitivity of VDRL and Meinicke Reaction BHADRA, A C (1955) *Indian med J*, **49**, 148 1 fig 2 refs

Relation between Serum Reactions for Syphilis and Immunization (Beziehungen zwischen Luesseroreaktionen und Immunisierungen) BOCKELER, R, and MAURER, H (1955) *Blut*, **1**, 121 20 refs

Technical Improvement for the More Rapid Extraction of Treponemata in the Nelson Test (Eine methodische Verbesserung zur schnelleren Extraktion der Treponemen beim Nelsontest) FEGELER, F, and KNAUFR, I (1955) *Zbl Bakt, I Abt Orig*, **162**, 540 4 refs

Modification by Sodium Salicylate of the Serological Reactions of Syphilis (Modifications apportees par le salicylate de sodium aux reactions serologiques de la syphilis) BOUJNAH, A, and DELAUNAY, A (1955) *Rev Immunol (Paris)*, **19**, 53 1 ref

First India Survey of Serological Tests for Syphilis CHACKO, C W, GAUB, W H, and GOPALAN, K N (1955) *Indian J vener Dis*, **21**, 1

SYPHILIS (Pathology)

Contribution to the Histology and Pathogenesis of Tabes Dorsalis (Contributo all'istopatologia e patogenesi della tabe) FLORIS, V, and PANSINI, A (1955) *Riv Neurol*, **25**, 1 17 figs, 22 refs

At the University Clinic for Nervous Diseases, Padua, the authors have examined in some detail the histological features of the spinal cord, spinal nerve roots, and meninges in six cases of tabes dorsalis On their findings, which are described, they base the hypothesis that the infection first attacks epidural structures, and thence proceeds to affect the meninges and finally the cord itself The paper is illustrated by a number of clear photomicrographs *L Michaelis*

SYPHILIS (Experimental)

Erythromycin ("Ilotycin"), Treponemes, and Experimental Syphilis in the Rabbit (Erythromycine (ilotycine), treponemes et syphilis experimentale du Lapin) DEROM, P, and VAN HOYDONCK, J (1955) *Rev belge Path*, **24**, 199 2 refs

Further Research on Experimental Syphilis in the Mouse (Nouvelles recherches sur la syphilis experimentale de la souris) GASTINEL, P, VAISMAN, A, and DUNOYER, F (1955) *Ann Derm Syph (Paris)*, **82**, 140

GONORRHOEA

Susceptibility of *Neisseria gonorrhoeae* to Eleven Antibiotics and Sulfadiazine Comparison of Susceptibility of Recently Isolated Strains with Results Obtained in Previous Years in the Same Laboratory DEL LOVE, B, and FINLAND, M (1955) *Arch intern Med*, **95**, 66 1 fig, 39 refs

The sensitivity of 108 strains of *Neisseria gonorrhoeae* to eleven antibiotics and to sulphadiazine was studied at the Thorndike Memorial Laboratory and Harvard Medical School, Boston Penicillin was the most effective of the agents tested and erythromycin, though considerably less active, came next, the remainder in order of sensitivity were oxytetracycline, tetracycline, chlortetracycline (aureomycin), chloramphenicol, carbomycin, streptomycin, neomycin, bacitracin, sulphadiazine, and polymixin B

A comparison of these findings with those of a similar investigation carried out in 1949 did not reveal any significant change in the sensitivity of the organisms to penicillin The authors state that any slight changes observed were well within the range of variability in the purity of the preparation used and the limits of experimental error in the method, which involved the inoculation of the organism on a series of agar plates containing doubling dilutions of the antibiotic The percentage of strains resistant to sulphadiazine in a concentration of 100 μg per ml was 84 in 1949 compared with nineteen in the present investigation, this is attributed to marked decrease in the use of sulphonamides in the treatment of gonococcal infection *John M Talbot*

Investigation of *Neisseria gonorrhoeae* by a Red Cell Sensitization Technique CHANARIN, I (1954) *J Hyg (Lond)*, **52**, 425 16 refs

An extract prepared from freshly isolated strains of *Neisseria gonorrhoeae* was shown to sensitize sheep erythrocytes so that they were haemolysed by a homologous antiserum prepared in the rabbit The author, working at the Central Pathological Laboratory, Durban, has investigated in detail the part played by the various components in the reaction, the techniques employed are fully described Of the various factors concerned in the adsorption of the antigen by the erythrocytes, one was shown to be the strength, within limits, of the extract Prolongation of the reaction beyond 30 min had little effect, most of the sensitization occurring within that time In a study of the effect of different temperatures it was shown that very little adsorption occurred at 4° C, the optimum temperature being 37° C The presence of electrolytes was necessary for the reaction It was found that all the antigen in the solution could be adsorbed by the erythrocytes even after repeated sensitization Strains of *N gonorrhoeae* which had undergone the "smooth to rough" (S–R) change were no longer capable of producing a sensitizing antigen The antigen was shown to be heat-stable and is thought to be probably polysaccharide in nature

Initially eighteen strains were examined, which by the mirror cross-absorption technique could be divided into two types, fifteen being of Type I and three of Type II, these types share a common antigen, and Type I has an additional antigen Examination of 67 further strains showed that 59 were of Type I and eight of Type II, while eight strains of meningococcus examined were found to have an antigen identical with the gonococcal Type I Of 28 strains of other neisseria, only one showed any cross-reaction with the gonococcal antiserum The author also demonstrated that the erythrocyte-sensitizing antigen did not fix complement, but that another antigen was present in the extract which did The application of these findings to human infection was felt to be outside

the scope of this study, but the author mentions that 30 per cent of patients with simple gonococcal urethritis gave a positive gonococcal haemolysis test, thus suggesting that the sensitizing haptene does play some part in the process of gonococcal infection In conclusion the author emphasizes the importance of the S–R change in any work on the antigens of *N gonorrhoeae*

[Recently Wilson (*J Path Bact*, 1954, **68**, 495, *Abstr Wld Med*, 1955, **17**, 435) described experiments in which he identified four group antigens and four type-specific antigens in gonococci He also discussed at length the S–R change and other changes in the agglutinability of the micro-organism] *R F Jennison*

Should Crede's Prophylaxis be Changed? (Soll die Crede sche Blennorrhoe-Prophylaxe abgeandert werden?) WALCH, E (1954) *Geburts u Frauenheilk*, **14**, 389

The extensive literature on the question whether silver nitrate or penicillin is a better prophylactic for blennorrhoea is very well summarized and discussed The author compared the results of prophylaxis with silver nitrate or with penicillin each in 100 newborn children and found a greater number (six) of non-specific conjunctivitis with penicillin than with silver nitrate (three) He concludes that penicillin is not a significantly better prophylactic, and that its use carries the risk of more resistent strains At the present time silver nitrate seems to be the best, although not the ideal, prophylaxis

W Leydhecker

Ophthalmia Neonatorum ORMSBY, H L (1955) *Canad med Ass J*, **72**, 576 5 tables, 13 refs

Conjunctival infections and chemical reactions in 8,418 newborn infants were noted The first 1,703 children were treated prophylactically with two drops of Sulmefrin (a solution of 0 5 per cent sodium sulphathiazole and 0 5 per cent sulphadiazine) in each eye following cleansing of the infant immediately after birth The next 1,570 children received 10 per cent sodium sulphacetamide to the conjunctival sac prophylactically The next 3,125 children received 1 per cent silver nitrate to the conjunctival sac, and the final 2,020 children had no treatment

Chemical reaction in the conjunctival sac of a small percentage of the children was caused by 1 per cent silver nitrate solution, but the incidence of staphylococcal, gonococcal, and inclusion conjunctivitis was low When no prophylaxis was used there was a slight increase in the incidence of gonococcal conjunctivitis The incidence of inclusion conjunctivitis was very similar to that when 1 per cent silver nitrate was used 1 per cent silver nitrate has stood the test of time as an efficient prophylactic for gonococcal ophthalmia and has no harmful effects [See also *Amer J Ophthal* 1955, **39**, 90]

C McCulloch

Ophthalmia Neonatorum SIVASUBRAMANIAM, P (1955) *J Jaffna clin Soc* **2**, 88 3 refs

A general article quoting recent cases, and emphasizing the need for prophylaxis with silver nitrate

P D Trevor-Roper

Standardization of Diagnostic Methods for Gonococcal Infections PARRINO, P S, O'SHAUGHNESSY, E J, and WHITE, J D (1955) *Amer J publ Hlth*, **45**, 457 9 refs

Ophthalmia Neonatorum SMITH, C A, and HALSE, L (1955) *Publ Hlth Rep (Wash)*, **70**, 462 20 refs

NON-GONOCOCCAL URETHRITIS AND ALLIED CONDITIONS

Notes on the Treatment of Nongonococcal Urethritis in Males with Tetracycline CLARKE, B G CHAIMSON, H, GOLDEN, H, and TASHIAN, H N (1955) *Bull Tufts–New Engl med Cent*, **1**, 34 5 refs

Results are reported from the Boston Dispensary of the treatment with tetracycline of sixteen males suffering from non-gonococcal urethritis The drug was given by mouth in doses of 250 mg four times daily for 5 days In all cases the urethral discharge disappeared within 1 to 5 days of the start of treatment and did not recur during the period of observation, which lasted from 1 to 3 weeks No untoward reactions to the drug were observed

The incubation period in these cases varied from 2 to 42 days From cultures of the discharge made in thirteen cases *Staphylococcus albus* was isolated Of ten strains of this organism tested, nine were sensitive to tetracycline *in vitro*, although the one patient with resistant organisms responded clinically Five of six tetracycline-sensitive strains of *Staph albus* were found to be resistant to sulphonamides

A further six patients with a non-gonococcal urethral discharge associated with prostatitis were also treated with tetracycline The urethral discharge ceased in all six cases, though two cases later relapsed owing to the emergence of organisms resistant to the antibiotic

R R Willcox

Etiology of Nongonococcal (Nonspecific) Urethritis WILLCOX, R R (1955) *J chron Dis* **1**, 381 42 refs

Writing from St Mary's Hospital, London, the author points out that the present high incidence of non specific urethritis and the lack of precise knowledge of its aetiology render it urgent that the causative organism should be identified without delay

Among the possible pathogens which have been considered are bacteria, trichomonads, spirochaetes, pleuropneumonia-like organisms (PPLO), and viruses He has found little difference in the bacterial flora in the urethra in treated and untreated cases, and in controls *Trichomonas vaginalis* has been reported by various workers to be present in from 5 to 29 per cent of cases, but the author feels that there is still insufficient evidence to incriminate *T vaginalis* in the majority of cases, although the successful experimental inoculation of the male urethra with cultures of this organism in a small number of volunteers reported by Lanceley and McEntegart (*Lancet* 1953, **1**, 668, *Abstr Wld Med*, 1953, **14**, 401) demands further research

It has been suggested that spirochaetes similar in morphology to those found in the mouth may be of importance, as they are in abacterial pyuria, but an inquiry carried out by the author suggested that the practice of oral or anal coitus was no more frequent among patients with non-specific urethritis than in the general population Much work has also been done recently on the relation of PPLO to non-specific urethritis, but these organisms have been found so often in healthy men and women that the author regards them as commensals

The blue staining inclusion bodies and red granules well known in the epithelial cells in trachoma have also been found in scrapings from the urethra of patients with so-called inclusion blennorrhoea and non-specific urethritis The author has therefore attempted to obtain additional evidence for a viral aetiology of non-specific urethritis by means of dermal and serological tests In a series of skin tests with antigens of the lymphogranuloma–psittacosis–trachoma group of viruses negative results were obtained with the psittacosis antigen, but with "lygranum" antigen and cat-scratch antigen positive results were slightly more frequent in cases of non-specific urethritis than in controls Complement-fixation tests for lymphogranuloma venereum and for enzootic abortion in ewes (due to a similar organism) gave no significant results Giemsa-stained urethral scrapings from a large number of patients, their female consorts, and from controls were examined for virus inclusion bodies elementary bodies, and PPLO The author concludes that none of these bodies can be incriminated as the cause of non-specific urethritis Finally, attempts to passage the virus or causal organism of non-specific urethritis into the brain or lungs of mice, subcutaneously into guinea-pigs, into the urethra, conjunctiva, or knee joints of baboons, or into embryonated hen's eggs were entirely unsuccessful The cause of non-specific urethritis therefore still remains to be discovered

V E Lloyd

Nonbacterial Regional Lymphadenitis ('Cat-scratch Fever") An Evaluation of the Diagnostic Intradermal Test McGovern, J J, Kunz, L J, and Blodgett, F M (1955) *New Engl J Med*, **252**, 166 4 refs

In an attempt to evaluate the use of skin-test antigens in the diagnosis of non-bacterial lymphadenitis ('cat-scratch fever') the authors carried out tests in eighteen clinical cases of the disease and in several groups of control subjects at the Massachusetts General Hospital, Boston Three antigens were prepared from pus aspirated from lymph nodes in three cases and a 0 1-ml dose was injected into the skin of the forearm of each subject tested Within 10 min a weal appeared which lasted 24 hrs in most cases, but this non-specific response had disappeared at 48 hrs The reaction was considered to be positive if there was an indurated papule 4 mm in diameter and a zone of erythema 1 cm or more in diameter

It was found that all the eighteen patients gave a positive reaction to one or more antigens A positive result was also obtained in four (10 5 per cent) of 38 members of the families of these patients, in one out of 21 members of healthy families, in four (22 2 per cent) of eighteen persons working in an animal hospital, and in one out of 22 members of the hospital staff The higher ratio of positive reactions in the personnel of the animal hospital, although suggestive, might easily be due to chance in the numbers tested

The authors conclude that the demonstration of positive reactions with skin-testing materials, as at present prepared, is of little value in the diagnosis of non-bacterial lymphadenitis in the absence of well-defined clinical signs and symptoms

Thomas Anderson

Reiter's Syndrome (In Dutch) Lindeboom, G A (1954) *Geneesk Gids*, **32**, 70 3 refs

This article, intended for the general practitioner, describes a case in a 23-year-old male with the complete triad Aureomycin improved the fever

J ten Doesschate

Non-Specific Urethritis and Reiter's Disease (In Dutch) Wentholt, H M (1954) *Ned T Geneesk*, **98**, 356 27 refs

Neurological Manifestations of Cat-scratch Disease Weinstein, L, and Meade, R H (1955) *Amer J med Sci*, **229**, 500 14 refs

Topical Use of Oxytetracycline in the Treatment of Non-Specific Urethritis (Uso topico della Terramicina nel trattamento delle uretriti aspecifiche) Ferulano, O, and Reda, T (1955) *G ital Chir*, **11**, 211 41 refs

CHEMOTHERAPY

Variations in the Antimicrobial Activity of the Tetracyclines II Reedy, R J, Randall, W A, and Welch, H (1955) *Antibiot and Chemother*, **5**, 115 6 refs

This is a continuation of an earlier investigation carried out at the U S Department of Health, Washington, D C (*Antibiot and Chemother*, 1954, **4**, 741, *Abstr Wld Med*, 1955, **17**, 95) into the activity *in vitro* of chlortetracycline (aureomycin), oxytetracycline, and tetracycline against a number of Gram-negative and Gram-positive organisms

Considerable differences in sensitivity to the three antibiotics were encountered in strains of *Staphylococcus*, *Aerobacter*, *Klebsiella*, *Escherichia*, *Salmonella*, *Shigella*, *Proteus*, and *Pseudomonas* Generally, chlortetracycline was the most effective against Gram-positive cocci and tetracycline the most effective against Gram-negative bacilli At some concentrations, however, oxytetracycline was more active than the other two against certain strains of organisms in both groups

The results indicate that these three antibiotics do not possess 'equal antibacterial activity" and that laboratory sensitivity tests are necessary to determine which will be the most effective in any particular infection The authors state that all three are equally effective

clinically against highly sensitive organisms—including *Haemophilus influenzae*, β-haemolytic streptococci, pneumococci, gonococci, and perhaps meningococci—and in diseases due to certain large viruses and to rickettsiae In the treatment of meningococcal meningitis tetracycline is of special value because it enters the cerebrospinal fluid more readily than chlortetracycline or oxytetracycline *Derek R Wood*

Changing Patterns of Resistance of Certain Common Pathogenic Bacteria to Antimicrobial Agents FINLAND, M (1955) *New Engl J Med*, **252**, 570 9 figs, 18 refs

From 1949 to 1954 inclusive a systematic study was undertaken at the Thorndike Memorial Laboratory, Boston, of the sensitivity to chemotherapy of a number of strains of pathogenic bacteria, and in the present paper the variations in drug resistance observed during this period are reported

There was no important change in resistance to the antibiotics then available of Group-A haemolytic streptococci, *Haemophilus influenzae*, or strains of meningococcus, gonococcus, and *Proteus* Strains of gonococcus isolated in 1954 were considerably more sensitive to sulphadiazine than those isolated in 1949, and this is attributed to the fact that penicillin had replaced sulphonamides in the treatment of gonococcal infections

Strains of *Staphylococcus aureus* collected and tested at various times over a period of 10 years showed not only a progressive increase in the proportion which were resistant to penicillin, but also an increase in the degree of resistance to the antibiotic About a quarter of the most recently isolated strains were moderately resistant to chlortetracycline , even in the first series of strains tested more than a quarter were highly resistant to oxytetracycline, which was assumed to be the result of cross-resistance against aureomycin None of the staphylococcal strains exhibited either a moderate or a high degree of resistance to chloramphenicol Strains of *Pseudomonas* showed a definite increase in resistance to streptomycin and to neomycin and a slight increase in resistance to the broad-spectrum antibiotics

The author states that most of the changes appeared to be directly correlated with the extensive use of the particular agent concerned, but some could only be explained on the basis of cross-resistance from other antibiotics *E G Rees*

Emergence of Antibiotic-resistant Gram-negative Bacilli SANDFORD J P , FAVOUR, C B , and MAO, F H (1955) *J Lab clin Med* **45**, 540 11 refs

At the Peter Bent Brigham Hospital, Boston the sensitivity to antibiotics of strains of recently isolated Gram-negative bacilli causing genito-urinary infections was compared with that of similar strains isolated before 1946 and maintained in a lyophilized state in the American Type Culture Collection It was shown that lyophilization in no way affected the antibiotic sensitivity of the organisms, which included *Aerobacter aerogenes*, various species of *Proteus*, *Escherichia coli*, *Pseudomonas aeruginosa*, and miscellaneous coliform bacilli They were cultured for 18 hrs in broth containing concentrations of streptomycin, chloramphenicol, chlortetracycline (aureomycin), or oxytetracycline ranging from 2 μg to 32 μg per ml The lowest concentration causing macroscopic inhibition of growth was regarded as the "sensitivity level", and strains not inhibited by 32 μg per ml were considered to be resistant All species showed an increased resistance to streptomycin, and *Aerobacter aerogenes* and strains of *Proteus* exhibited a significantly increased resistance to chlortetracycline and oxytetracycline However, there did not appear to be any change in the number of strains which were sensitive to chloramphenicol *E G Rees*

PUBLIC HEALTH AND SOCIAL ASPECTS

Further Contributions to the Existence of an Antigenic Affinity between the Agents of Trachoma and those of Lymphogranuloma Venereum and Psittacosis (Ulteriori contributi sull esistenza di affinita antigeniche fra gli agenti del tracoma e quelli del linfogranuloma venereo-psittacosi) BABUDIERI, B BIETTI G B , and PANNARALE, M R (1954) *Boll Soc ital Biol sper*, **30**, 1348 5 refs

The serum of patients with trachoma gave a positive reaction with the ornithosis-psittacosis antigens only four times out of 21 It was thought that the level of trachoma antibodies in the serum might be very low and a trachoma antigen was prepared from conjunctival scrapings This gave a positive reaction in nine out of nine cases with trachoma serum, four out of four cases of lympho granuloma serum, and thirteen out of seventeen cases of psittacosis *D Maurice*

Venereal Disease among Teen-agers Its Relationship to Juvenile Delinquency DONOHUE, J F , GLEESON, G A , JENKINS, K H , and PRICE, E V (1955) *Publ Hlth Rep (Wash)*, **70**, 453 11 figs, 3 refs

This paper gives the results of a statistical analysis of special reports submitted to the Venereal Disease Program of the U S Public Health Service by State and city health departments giving the age incidence among cases of syphilis and gonorrhoea reported in the year 1953

The occurrence of infectious venereal disease among persons less than 20 years of age in the various States and in the country as a whole is illustrated in tables and figures, and the relation between the incidence of venereal disease in this age group and certain socio economic factors is shown in scatter diagrams

A significant positive association is shown to exist between the incidence of venereal disease in persons under 20 and the number of defendants in criminal proceedings for Federal offences in the same age group promiscuity as indicated by the illegitimacy ratio for all live births, proportion of reported foetal deaths where the mother s age was less than 20, and the proportion of low-income families in the general population A significant association is shown to exist between the incidence of juvenile venereal disease and the percentage school enrolment in the same age group

In discussing these findings the authors point out that they are open to several interpretations It is arguable that it is only natural that sexually active adolescents would account for a substantial proportion of all venereal infections But ' a youngster infected with a venereal disease has obviously deviated from the accepted pattern of approved social behaviour In this sense, venereal disease itself might be considered a manifestation of the broad problem of juvenile delinquency

Benjamin Schwartz

Congenital Syphilis Medico-Social Problems as Seen in the Provincial Child Welfare Institutes in Italy (La sifilide congenita I problemi medico-sociali nella sifilide congenita visti attraverso gli I P A I) VITETTI, G , and MENICHELLA, V (1955) *Pediatria (Napoli)*, **63,** 345 3 figs

Wanted, a National Programme for the Control of Venereal Diseases RAJAM, R V (1955) *Antiseptic*, **52,** 413

Venereal Disease Statistics (Zur Geschlechtskrankenstatistik) RACHOLD, R (1955) *Öff GesundhDienst*, **17,** 41

Medical Evaluation of a System of Legalized Prostitution LENTINO, W (1955) *J Amer med Ass*, **158,** 20 3 refs

Tetracycline (Tetracyn) in the Treatment of Donovanosis MARMELL, M , and PRIGOT, A (1955) *Harlem Hosp Bull*, **8,** 9 4 figs, 4 refs

Etymology of the Term " Syphilis " SPITZER, L (1955) *Bull Hist Med*, **29,** 269

Serological Study of Yaws in Java HUAN-YING, LI, and SOEBEKTI, R (1955) *Bull Wld Hlth Org* **12,** 905 11 figs

Decline and Fall of Syphilis in New York State III Early Acquired Syphilis VOUGHT, R L , MELLO L DE, and LOCKE, F B (1955) *J chron Dis*, **2,** 303 3 figs, 3 refs

MISCELLANEOUS

Common Problem of Venereal Warts GLENN, J F (1955) *U S armed Forces med J*, **6,** 983 12 refs

INDEX TO VOLUME XXXI, 1955

Authors and subjects of articles in the body of the Journal are indexed together There is a separate index to subjects of articles abstracted and another to authors of articles abstracted

INDEX TO SUBJECTS OF ARTICLES ABSTRACTED

** denotes that only the title is included with the abstracts*

INDEX TO AUTHORS OF ARTICLES ABSTRACTED

** denotes that only the title is included with the abstracts*

pattern of results among fourteen mothers of congenitally syphilitic children (Wilkinson and Sequeira, 1955)

Table VI shows the incidence of positive TPIs associated with negative STS in patients attending the Royal Free Hospital The totals indicate the total number of sera received by stage of syphilis In early and latent syphilis, treatment results in a considerable proportion of cases with negative STS and positive TPI Among patients attending hospital with late symptomatic syphilis, and representing in general a later age group, a proportion have negative STS and positive TPI Of fifteen untreated patients with cardiovascular or neurosyphilis, three had this pattern of results, one of these having aortic incompetence with radiological appearances supporting a diagnosis of syphilitic aortitis A later specimen of serum from this patient had a positive Wassermann reaction and a negative Kahn test and Price's precipitation reaction The other two cases had tabes dorsalis in one, the

TABLE VI
CASES OF SYPHILIS FOUND TO HAVE NEGATIVE STS AND POSITIVE TPI

Diagnosis Syphilis	No Untreated		No Treated	
	Total	STS− TPI+	Total	STS− TPI+
Early	13	0	81	16
Latent	—	?	121	28
Of cardiovascular system	6	1	6	1
Of central nervous system	9	2	22	10
Congenital	0	0	34	3

condition was of long standing and may no longer have been active, and in the other the cerebrospinal fluid changes indicated an active infection

From these results it appears that the TPI may be positive in association with negative STS in active syphilis The TPI in patients with no signs or history of syphilis reveals a proportion of positive results Those with positive STS are treated as latent syphilis The exact status of those with negative STS is still in doubt, but it would appear probable that a proportion represent active infections

SUMMARY

The reproducibility of the Treponemal Immobilization Test from a laboratory aspect and in routine use is comparable to that of the STS

While there are as yet insufficient reports of results on non-syphilitic sera for an absolute assessment of specificity, the results so far available indicate that the TPI is highly specific for the treponematoses It appears likely that a proportion of patients with negative STS and positive TPI may represent a form of latent syphilis

Our thanks are due to the directors of the Clinics of the Royal Free and London Hospitals for access to clinical records, to Dr I N Orpwood Price for his advice and encouragement, and to our technicians, Mrs A Chaffe and Mr A D Lucas, for their assistance in performing the test

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STUDIES ON THE TREPONEMAL IMMOBILIZATION TEST

III USE OF THE TPI AS A VERIFICATION TEST IN SUSPECTED LATENT SYPHILIS*†

BY

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In latent syphilis the diagnosis frequently rests purely on serological grounds, there being no clinical or epidemiological evidence to corroborate the serological findings In these circumstances, a great responsibility rests upon the serological tests employed, and an enormous volume of research has been directed to raising the sensitivity of these tests to as high a level as possible without compromising their specificity The application of serum testing on a mass scale to presumably healthy populations with a view to discovering unsuspected cases of syphilis has emphasized the paramount importance of specificity, and it has been suggested (Kahn and McDermott, 1953) that too much stress has been laid upon the sensitivity of tests at the expense of their specificity This view is borne out by the results given by routine tests performed before demobilization which showed 75,000 American servicemen to be sero-positive, who were known to be sero-negative on entry into the services and who had no history of venereal infection Sample surveys showed that of those who were again found to be sero-positive on re-testing, more than half had probable biological false positive reactions (Moore and Mohr, 1952a)

Although this American experience may have focused attention on the problem, dissatisfaction with serum tests for syphilis (STS) using lipoidal antigens has long been felt, as shown by the numerous verification tests which have been devised in the past In general, these have been based on alterations in the physical conditions of the tests, but have used the same lipoidal antigens, and none has proved generally satisfactory Tests using lipoidal antigens are usually said to be non-specific in the sense that they do not represent a reaction between an antibody and the causative organism of the disease However, there is some evidence that the virulent Nichols strain of *T pallidum* may contain a component responsible for reagin production (Hardy and Nell, 1955), and similar findings have been reported for the avirulent Reiter treponeme by the Italian school of serologists (D'Alessandro, Oddo, and Dardanoni, 1950) Attempts to use virulent *T pallidum* as an antigen, and hence realize a specific test, have been hampered by continued failure to grow the organism *in vitro* Tani and Asano (1951) described an agglutination test using killed treponemes of the Nichols strain extracted from the testes of infected rabbits This work attracted little attention at the time and it was not until Nelson and Mayer (1949) developed the Treponemal Immobilization Test (TPI) that interest in techniques using virulent treponemes was re-awakened The TPI test shows the presence of an antibody in syphilitic serum clearly acting on the parasite and requiring complement for its action It is highly specific for treponemes of the syphilis-yaws-bejel group, and from its inception it was clear that it might find a useful application in patients with suspected latent syphilis to differentiate true syphilitic reactions in tests using lipoidal antigens from "biological false positive" or non-specific reactions (NSR)

Any verification test designed for use in this connexion must fulfil certain criteria

(*a*) It must be specific for treponemal infection and reproducible These aspects of the TPI have been reviewed by Zellmann (1954) and by Sequeira and Wilkinson (1955)

(*b*) Its sensitivity should be sufficiently high to give positive reactions in all cases of latent syphilis

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†Based on an address given to the M S S V D on February 25 1955

(*c*) Ideally, it should be unaffected by treatment so that it can give a retrospective confirmation of the original diagnosis where treatment has been given

(*d*) It should give a clear-cut "yes or no" answer with the minimum of doubtful or indeterminate results

Although patients with latent syphilis have been included in many of the surveys of the results given by the TPI at various stages of syphilis, in some of the literature it is not clear whether the diagnosis of "latent syphilis" rested solely on serological findings or whether there was other evidence to substantiate it The incidence of negative TPI results also varies widely in different reports The principal aim of the present investigation was to establish the performance of the TPI in patients with proved latent syphilis, and to see how it fulfilled the criteria of a verification test outlined above The test has also been applied to patients with "latent syphilis" attending two venereal disease clinics and to the examination of a large number of "problem sera"

Technique and Clinical Material

The Treponemal Immobilization Test technique used closely followed that originally described by Nelson and Mayer (1949) with the minor modifications noted in a previous paper (Wilkinson, 1954b) For convenience of description, the sera tested have been divided into the following groups

(*a*) Sera from patients with latent syphilis where the diagnosis rested on other evidence besides the serological findings

(*b*) Patients with latent syphilis attending the Whitechapel Clinic, London Hospital, and the Venereal Diseases Department of the Royal Free Hospital

(*c*) "Problem" sera sent to the Venereal Diseases Reference Laboratory (Medical Research Council) from patients whose STS had been found positive on routine testing in other laboratories

(*d*) Sera from patients with leprosy, lupus erythematosus, or haemolytic anaemia, conditions in which non-specific STS reactions are thought to be frequent

On receipt in the laboratory, sera were separated and divided into two portions One was stored at −20° C until the TPI test could be carried out, and four STS were performed on the other,

(1, 2) Wassermann Reactions with crude heart extract and cardiolipin antigens, using the Whitechapel technique (Price, 1950)

(3) Standard Kahn Test

(4) Price s Precipitation Reaction (PPR) (Price, 1948)

In the case of the Royal Free Hospital patients, the cardiolipin WR was not used, but the STS and TPI techniques used were the same as in the V D Reference Laboratory

In all cases where the TPI result was at variance with the STS or with the clinical findings, the TPI was repeated on the same specimen of serum, and whenever possible a second specimen was obtained from the patient concerned Doubtful TPI tests were repeated at least twice on the same specimen before being reported as such

Evaluation of the TPI Test in Patients with Confirmed Latent Syphilis

The patients in this group showed no clinical signs of syphilis, but the diagnosis of latent syphilis was supported by other evidence than the serological findings Four types of patients were accepted for inclusion in this study

(*a*) Mothers who had given birth to congenitally syphilitic children

(*b*) Patients who gave a clear history of lesions of early syphilis for which no treatment or only very inadequate treatment had been given at the time

(*c*) Patients whose consorts were also sero positive or who showed evidence of late syphilis

(*d*) Patients with asymptomatic neurosyphilis These may not necessarily be representative of latent syphilis without central nervous system involvement, but they were included because the diagnosis rests on good grounds and the disease is *clinically* latent

In many instances patients qualified for inclusion under more than one of the categories listed above

Sera from both treated and untreated patients were examined, a comparison of the STS and TPI results is given in Table I In this and subsequent Tables "STS +" means that all four STS were positive, "STS 0" that all were negative, and "STS ±" that some were positive and others negative

TABLE I

RESULTS OF TPI TESTS ON 136 PATIENTS IN WHOM THE DIAGNOSIS OF LATENT SYPHILIS RESTED ON OTHER EVIDENCE THAN STS FINDINGS

Category	Treatment	No of Patients	STS			TPI		
			+	±	0	+	±	0
Mothers of congenitally syphilitic children	Untreated	14	7	2	5	13	1	—
	Treated	26	14	3	9	25	—	1
History of early syphilis	Untreated	6	5	—	1	6	—	—
	Treated	2	2	—	—	2	—	—
Consorts sero positive or other evidence of syphilis	Untreated	31	20	8	3	29	2	—
	Treated	35	18	8	9	35	—	—
Asymptomatic neuro syphilis	Untreated	6	4	2	—	6	—	—
	Treated	16	10	3	3	16	—	—

Sera from 136 patients were examined, in 132 of whom the TPI was positive Three patients, all untreated, gave a doubtful TPI result One was a woman whose husband had latent syphilis, and her TPI result was confirmed on two subsequent specimens of serum The second patient had a history suggestive of secondary syphilis 26 years previously and had the scar of a penile sore, his

wife was also sero-positive The third patient had given birth to a congenitally syphilitic child The diagnosis of latent syphilis seems to rest on good grounds in the last two cases and to be highly probable in the first

Only one patient in the series gave a negative TPI test, the clinical history was as follows *

A female, aged 32, was found to be sero-positive in 1942 after the birth of a child which died of '?diphtheria' at the age of 1 month She was treated with four courses each of 0 45 g N A B and 0 2 g Bi weekly for 10 weeks and became sero-negative In June, 1945, she was delivered of a male child which developed snuffles and a rash when 1 month old It was found to be sero-positive, and was treated by oral stovarsol and later by penicillin In 1954 the child's STS were negative and the spinal fluid normal, the only abnormal clinical findings were unequal pupils which did not react to light On March 11, 1955, the child s STS were negative, but the TPI test was positive

A month after delivery the mother s serum reactions were found to be positive again and she was re-treated with two further courses of N A B and bismuth In December, 1946, she was delivered of a healthy boy who has remained sero-negative over 7 years of observation STS and TPI tests were carried out on the mother on November 19, 1954, and on March 11, 1955, and were negative on both dates

In some of the published work on the results given by the TPI in latent syphilis it is not clear whether the diagnosis rested on serological grounds alone or whether it was supported by other evidence However, Miller, Slatkin, Brodey, Wechsler, and Hill (1954) found the TPI positive in fourteen problem sera where there was other evidence of syphilis besides the STS Zellmann (1954) found that ten women who had given birth to congenitally syphilitic children were all TPI-positive, and that 64 out of 66 patients with treated asymptomatic neurosyphilis were TPI-positive, one being doubtful and one negative These last two patients were early cases of less than 2 years' standing Nelson, Zheutlin, Diesendruck, and Austin (1950) found that fourteen patients with asymptomatic neurosyphilis were all TPI-positive, while Edmundson, Olansky, Wood, and Kamp (1955) reported 44 cases of this condition (23 of whom had been treated) who gave positive or doubtful reactions with the TPI test

Although the present series is small, the results show that a negative TPI result was found in less than 1 per cent of the patients with confirmed latent syphilis and it should be noted that this one patient had been treated, judging from the history, this treatment was probably given early in latency Since doubtful TPI tests were found among the untreated patients, it is possible that negative TPI reactions may occur in untreated latent syphilis, but the data available at present suggest that this must be a very rare occurrence

As far as can be judged by qualitative tests, previous treatment seems to have little effect on the TPI Zellmann (1954) has suggested that, on analogy with the behaviour of reagin, immobilizing antibody may disappear from patients treated early in latency, but the difficulty of dating the infection makes this possibility hard to evaluate

When a positive TPI test is obtained in patients in whom the only suggestion of latent syphilis comes from the finding of positive STS, it is felt that the demonstration of immobilizing antibody confirms past treponemal infection although it does not necessarily imply present activity of the disease process A negative TPI test, confirmed by repetition on a second specimen of serum to exclude technical error and the possibility of a developing early syphilis, suggests very strongly that the positive STS are non-specific in nature, particularly when the patient has not received any penicillin therapy for other conditions in the past The interpretation of a negative TPI test in patients treated for presumed latent syphilis is less certain While it may mean that the original diagnosis was founded in error on non-specific STS reactions, there is as yet no detailed information from serial TPI tests on large numbers of individual patients of the frequency of TPI-reversal in latency In default of this, the interpretation of negative results must, of necessity, be cautious

Results of TPI Tests on Patients with Suspected Latent Syphilis attending a Venereal Disease Clinic

TPI tests have been carried out as an adjunct to the routine STS performed on new patients with suspected latent syphilis attending the Whitechapel Clinic at the London Hospital since July, 1952, and the Venereal Diseases Department of the Royal Free Hospital since January, 1953, and also on patients treated for latent syphilis in the past as they attended again for observation The present review covers those patients tested up to the end of 1954 and includes those previously reported by Wilkinson (1954b) The comparative results given by the two types of test are shown in Table II (overleaf)

The untreated group of 200 patients included 23 (seventeen females and six males) who gave positive reactions with one or more of the STS, but whose TPI tests were negative, suggesting that the STS reactions were non-specific STS had originally

*I am indebted to Dr A E Tinkler of the Royal Cornwall Infirmary Truro for supplying these clinical details

TABLE II

RESULTS OF PARALLEL STS AND TPI TESTS ON PATIENTS WITH SUSPECTED LATENT SYPHILIS ATTENDING V D CLINICS

Treatment	No of Patients	STS	TPI		
			+	±	0
Untreated	200	+	135	—	5
		±	29	—	18
		0	4	—	9
Treated	248	+	130	2	10
		±	46	—	1
		0	52	—	7

been performed because of pregnancy (eight cases), blood donation (two cases), emigration (three cases), gonorrhoea or urethritis (three cases), venereophobia (two cases), and one case each of bronchitis, thyrotoxicosis, retinal oedema ? collagen disease, and pyrexia of uncertain origin One patient was referred by a private doctor and no details are available Both STS and TPI were negative in nine patients, these had given positive STS on previous specimens and probably represent transient non-specific reactions of unknown causation, or technical false positive reactions due to errors in the performance of the STS

Altogether 248 patients had been treated for latent syphilis in the past, and of these eleven (ten females and one male) gave positive reactions with one or more of the STS while the TPI was negative, suggesting that the STS reactions might be non-specific Seven had been found sero-positive during pregnancy and two were subsequently found to have lupus erythematosus, L E cells having been demonstrated One had been found sero-positive and treated 13 years previously, another had been treated 2 years previously because of positive STS found as a blood donor, she remains sero-positive The remaining female patient was aged 72 and was found to be sero-positive during investigation of pain in the back, attributed to osteo-arthritis The only male patient had an abrasion of the leg in 1944, which failed to heal, and on investigation his STS were found to be positive Despite very intensive treatment his STS have increased in titre, he also has nephritis and hypertension

Seven of the treated patients gave negative STS and TPI tests In four, reversal of the STS occurred very rapidly after the institution of treatment One patient had been treated on serological grounds in 1943, but there was a history suggestive of early syphilis 1 year previously In another case, the patient had had a congenitally syphilitic child in 1941 which died 4 months after birth It seems probable that these patients were treated early in latency, and this may account for the negative TPI results

The number of female patients showing the STS-positive-TPI-negative pattern suggesting non-specificity of the STS greatly exceeded the males showing similar results This is partly accounted for by the Royal Free Hospital patients who were nearly all females In the London Hospital patients the sex difference was not significant An analysis of the patients attending the latter hospital with reference to their racial origin showed that 43 were non-European, mainly West Africans and West Indians Only one of these, an Indian, showed the pattern suggesting non-specificity of the STS In some of these coloured patients the positive STS and TPI reactions may well have been due to infection with yaws in childhood, as suggested by Laird (1955), but the TPI test is not of value in differentiating between the treponematoses

If the finding of a negative TPI test is an acceptable criterion of the non-specificity of the STS reactions, 11 5 per cent of the untreated patients and possibly 4 4 per cent of those who had been treated for latent syphilis showed non-specific results with the serum tests using lipoidal antigens They are of the same order as those reported by Chacko (1953) from St Mary's Hospital, London, who found that nine out of 101 patients with treated latent syphilis showed negative TPI tests The results obtained by other workers with sera from patients with latent syphilis and with "problem" sera are summarized in Table III

TABLE III

PROPORTION OF TPI NEGATIVE SERA REPORTED IN PATIENTS WITH LATENT SYPHILIS AND IN PROBLEM SERA

Author	Date	No of Cases	Diagnosis	TPI Negative (per cent)
Magnuson and Thompson	1949	106	Early latent	0
		20	Late latent	0
Nelson and others	1950	51	Latent	0
Durel and others	1952	332	Treated latent	27
Miller and others	1952	37	Early latent	0
		213	Late latent	4
Moore and Mohr	1952	300	? Latent ? NSR	45
Nelson	1953	496	Untreated ? Latent ? NSR	42
Gate and others	1953	493	Treated latent	27
Miller and Smith	1953	773	Problem sera	36
Chacko	1953	101	Treated latent	9
Crampon and Baelden	1953	91	Latent	17
Miller and others	1954	30	Early latent	0
		139	Late latent	0
Ledbetter	1954	1 793	? Latent ? NSR	43
Present Series	Clinic patients	200	Untreated latent	11 5
		248	Treated latent	4 4
	—	427	Problem sera	28

These widely varying figures are probably explained by factors such as the criteria of selection, the varying incidence of syphilis in the populations from whom the patients were drawn, the proportion of treated patients, the possible influence of treatment in early latency, and the types of STS employed

Results given by the TPI Test in "Problem Sera"

These sera came from patients who had been found sero-positive at other laboratories on routine testing Specimens were sent to the V D Reference Laboratory either because the original STS had given anomalous results or because the results were at variance with the clinical findings For descriptive purposes they have been divided into two main classes

(*a*) Presumably healthy patients, blood donors (71) and pregnant women (278)

(*b*) Patients in hospital for a variety of complaints in whom routinely performed STS had been found positive

It must be emphasized that, because an unknown degree of selection by the physicians may have occurred when sending the sera for a second opinion, the results obtained are not necessarily representative of the types of patients tested It is probable, for instance, that sera giving weakly positive or discordant STS results would have been sent for checking rather than those giving strongly positive and concordant STS results

Blood Donors—94 sera* from 74 patients were examined In three sera no valid test could be obtained with the TPI, and in two the complement-fixation tests were anticomplementary Excluding these, the comparative STS and TPI results are shown in Table IV

TABLE IV

RESULTS OF PARALLEL STS AND TPI TESTS ON 69 BLOOD DONORS FOUND SERO POSITIVE ON ROUTINE SERUM TESTING

STS	TPI		
	+	±	0
+	29	1	9
±	11	—	15
0	—	—	4

There was agreement between the STS and the TPI in sera from 45 patients, in 24 (35 per cent), however, one or more of the STS were positive, but the TPI was negative, suggesting that the positive STS reactions were non-specific Analysis of the results by sex showed that this was without effect Fourteen of the patients had been treated on the basis of the positive STS findings, but the incidence of STS-positive-TPI-negative results was the same in the treated and untreated groups This incidence of presumed non-specific reactions is much lower than that reported by Stokes, Boerner, Hitchens, and Nemser (1946) These authors found that 489 (0 23 per cent) out of 210,261 donors at the Philadelphia Blood Donor Center tested between January and September, 1944, gave definite positive STS reactions The donors were predominantly white, the series including only 2,579 negroes, and the incidence of sero-positivity was below that reported for the area (0 5 per cent) Extensive clinical and serological investigations were carried out on a sample of 79 patients said to be "essentially unselected" of the 489 sero-positive donors, only 40 5 per cent were finally adjudged to have syphilis, the remaining 59 5 per cent being considered to have given non-specific STS reactions

In most of the patients now reported, the positive STS were found when they volunteered as blood donors, so that they represent positive STS reactions in presumably healthy patients, and any possible effect of repeated donation of blood in the causation of non-specific STS reactions can be excluded

Pregnancy—This group included 309 sera* from 279 patients in whom the STS and TPI results could be compared In 35 patients, the STS had been found positive during pregnancy in the past, and the TPI was carried out at periods varying from 5 months to 8 years after delivery Thirty-three of the patients had been treated Comparative results of the two types of test are shown in Table V

TABLE V

RESULTS OF PARALLEL STS AND TPI TESTS ON 35 PATIENTS FOUND SERO POSITIVE DURING PREGNANCY IN THE PAST

STS	TPI		
	+	±	0
+	16	—	5
±	8	—	2
0	2	—	2

In the remaining 244 patients who had been found sero-positive on routine antenatal testing, the TPI was carried out during pregnancy or the puerperium Results of the parallel tests are given in Table VI (overleaf)

Altogether 211 of the patients were untreated at the time of testing, 27 had been treated during the

*This figure includes 27 donor sera previously reported (Wilkinson 1954b)

*Includes 97 pregnancy sera previously reported (Wilkinson 1954b)

TABLE VI

RESULTS OF PARALLEL STS AND TPI TESTS ON 244 PATIENTS FOUND SERO POSITIVE ON ROUTINE TESTING DURING PREGNANCY

STS	TPI		
	+	±	0
+	108	2	21
±	33	1	46
0	3	1	29

pregnancy, and six had received antisyphilitic treatment in the past, two during a previous pregnancy There was agreement between the STS and TPI in 173 sera and disagreement in 71 Four patients gave negative STS reactions, while the TPI was positive in three and doubtful in one Two of these patients had given positive STS reactions on previous specimens, another gave a history of anomalous STS reactions in a previous pregnancy and a fourth had had inadequate treatment for syphilis 9 years previously In the remaining 67 sera showing disagreement, one or more of the STS were positive while the TPI was negative, suggesting that the positive STS reactions were non-specific in nature This represents 27 5 per cent of the total 244 sera in the group It is usually held that where the STS give concordant results among themselves, the results are more likely to be specific than when the results are discordant In 131 sera all four STS were positive, and of these 21, or 16 per cent, were TPI-negative In marked contrast to this, 46 (57 5 per cent) of the eighty sera giving discordant STS results were TPI-negative, suggesting that the STS reactions were non-specific The relationship between the strength of the STS reaction, as judged by the PPR titre, and the outcome of the TPI is shown in Table VII

TABLE VII

COMPARISON OF THE PPR TITRE AND THE TPI RESULT IN 244 ANTENATAL SERA

TPI	PPR Titre							
	0	Neat	2	4	8	16	32	64
Positive*	22	60	29	13	13	6	5	2
Negative	65	21	6	1	1	—	—	—

*Four sera which gave doubtful TPI results have been included in the positive group

Both treated and untreated patients have been included in this analysis It is clear that, as the PPR titre rises, the proportion of sera found to be TPI-negative falls off sharply, the bulk of the presumed non-specific reactions occurring at titres of 2 and under

Because of the unknown element of selection in these patients, the figure of 27 5 per cent presumed non-specific reactions does not necessarily represent the incidence of such reactions to be found in routine antenatal testing Small series have been reported by Ranque, Gallais, Depieds, and Moignoux (1953) who carried out TPI tests on all antenatal sera found to be STS-positive, and found six out of eighteen to give negative reactions with the TPI test Wheeler, Van Goor, and Curtis (1954) found 29 out of 39 pregnancy sera which were thought to show acute biological false positive reactions to be TPI-negative Pigeaud, Sohier, Thivolet, Richard, and Rolland (1954) reported the results of TPI tests on 32 antenatal sera found to be STS-positive on routine testing The TPI was negative in four out of sixteen patients in whom the STS gave concordant results, and negative in thirteen out of sixteen patients in whom the STS gave discordant results

In an attempt to estimate the absolute incidence of non-specific reactions in *unselected* antenatal sera, one of us (P J L S) has carried out routine TPI tests at the Royal Free Hospital during 1953 and 1954 on *all* antenatal sera which gave positive STS reactions Out of 2,512 patients tested, 29 (1 15 per cent) were found to be STS-positive Ten of these had been referred from the Venereal Diseases Department, and only one of these was TPI-negative The remaining nineteen patients were first found sero-positive on routine antenatal testing, and four of these were TPI-negative Although the numbers of STS positive patients are small, they suggest that an appreciable proportion, of the order of one-fifth, of positive reactions first revealed by routine antenatal testing, may be non-specific This estimate is in fair agreement with the findings of 27 5 per cent presumed non-specific reactions in the larger group of pregnancy sera described previously

Although the *absolute* incidence of non-specific reactions is probably very low, about 1 in 500 on the above figures, this is of small help to the clinician faced with a patient who *has* been found sero positive, here, the *proportion* of positive STS reactions in pregnancy which are non specific is of much greater importance than the absolute incidence Even though this is very low, the extensive use of routine antenatal testing must produce, in the aggregate, a very large number of problem ' sera in which the use of the TPI test can be of great help

There is little or no information about the behaviour of the STS after the end of pregnancy in TPI-negative patients with presumed non-specific STS reactions In some patients who have been retested after pregnancy they have been negative,

suggesting that they were of the acute type, but in others they are known to have persisted for several years In the present series, eight patients were known to have given anomalous STS reactions during a previous pregnancy In six, one or more of the STS were positive when the patient was again tested during pregnancy, and in one who was STS-negative when the TPI was performed, the STS had been positive on a previous specimen The TPI was positive in three and doubtful in one patient and negative in four, one of whom had been treated 3 years previously during pregnancy

Diseases Other than Syphilis—The preceding groups of blood donors and pregnant women represent presumably healthy persons subjected to routine serum testing A further 149 patients were suffering from a variety of diseases other than syphilis, and were found to be STS-positive on routine examination, there being no definite clinical evidence suggesting syphilis The results of parallel STS and TPI tests are shown in Table VIII

TABLE VIII

RESULTS OF PARALLEL STS AND TPI TESTS ON 149 PATIENTS WITH DISEASES OTHER THAN SYPHILIS WHO WERE FOUND SERO POSITIVE ON ROUTINE TESTING

STS	TPI		
	+	±	0
+	75	—	8
±	17	—	36
0	1	—	12

Taking the group as a whole, one or more of the STS was positive and the TPI negative in 44 patients (29 per cent) As in the sera from donors and pregnant women, the majority of the STS-positive-TPI-negative results were found where there was discord among the STS results, 36 (68 per cent) of the 53 sera of this type being TPI-negative, suggesting that the STS results were non-specific

The patients were suffering from a wide variety of complaints, but the numbers with any one disease were too small to warrant analysis Seventeen of the patients had gonorrhoea and were found sero-positive on routine testing, the TPI was positive in all but one Nine patients had non-gonococcal urethritis, and in five of these the TPI was positive

Some clinical conditions have been recognized to be associated with non-specific STS reactions which persist for long periods This seems to be well established in lupus erythematosus, leprosy, and the form of haemolytic anaemia due to auto-antibody production These conditions have therefore been excluded from the preceding group and are presented separately in Table IX *

Sera from these patients were examined irrespective of whether their STS had previously been found positive Although the numbers are small, it is

TABLE IX

RESULTS OF PARALLEL STS AND TPI TESTS IN LUPUS ERYTHEMATOSUS LEPROSY AND ACQUIRED HAEMOLYTIC ANAEMIA

Disease	No of Cases	STS	TPI Results		
			+	±	0
Lupus Erythematosus	20	+	1	—	7
		±	—	—	3
		0	—	—	9
Leprosy	18	+	4	—	7
		±	—	—	4
		0	—	—	3
Acquired Haemolytic Anaemia	9	+	—	—	3
		±	—	—	3
		0	—	—	3

clear that even sera which gave positive results with all four of the STS were, for the most part, TPI-negative while all of the sera giving discordant STS results were negative with the TPI test

Lupus Erythematosus—Positive STS were found in eleven of the patients with various types of lupus erythematosus, while the TPI was positive in one

A female, aged 57, was found to have gummatous ulcers of the uvula and soft palate in 1948 Her STS were strongly positive and the CSF normal Response to treatment with bismuth and penicillin was satisfactory, the STS titre dropping from 256 to 8 In 1952 she developed a rash on the face which was diagnosed as chronic discoid lupus erythematosus

The appearance of non-specific STS reactions does not seem to be directly related to the severity of the lupus erythematosus, as one patient who had completely negative STS had very severe manifestations of generalization of the disease, from which she died shortly afterwards The positive STS reactions may be present before the signs of lupus erythematosus develop Haserick and Long (1952) found positive STS reactions in seven out of 29 patients, only one of whom had a history of syphilis They described five patients in whom periods of up to 7 years elapsed between the finding of positive STS reactions and the development of lupus erythematosus In the present series, two patients, who were found to have positive STS reactions on routine antenatal testing, were subsequently found to have lupus erythematosus, the diagnosis being confirmed by the finding of L E cells One developed hepatitis and nephritis which

*These include the cases previously reported (Wilkinson 1954b)

resulted in the death of the foetus She was treated with 10 mega units penicillin, but the positive STS have persisted for 4 years The second patient was known to have been sero-negative during pregnancy in 1949 and had had pneumonia which had been treated with penicillin In 1951 she again became pregnant and her STS were found to be positive She showed no clinical evidence of syphilis, but was treated with ten weekly injections of 0 3 g bismuth followed by 6 mega units penicillin The child was stillborn In 1953 she developed arthritis, and on investigation was found to have disseminated lupus erythematosus

The earlier literature on non-specific STS reactions in this condition has been reviewed by White (1947), who reported three cases, and by Gold and Gowing (1953) Rein and Kostant (1950) found one or more of a battery of six STS positive in 63 out of 178 patients with various types of the disease They noted that 83 per cent of the sera were anticomplementary in one or both of the complement-fixation tests used, but found no evidence that the sera giving positive STS reactions specifically showed increased gamma globulins Zellmann (1952) examined 83 patients with disseminated lupus erythematosus, and found that thirteen gave positive and two doubtful reactions with one or both of two STS used Only one of these fifteen sero-positive patients had " proved " syphilis, the other fourteen being thought to show possible non-specific reactions

Leprosy —This disease has long been thought to be associated with non-specific serum reactions for syphilis Sera from eighteen lepers were examined , except for five sera sent from Malta, all were from patients resident in Great Britain Fifteen were positive with one or more of the STS, but, of these, only four were TPI-positive One was a West African who also has neurosyphilis, the second was a young Filipino woman who also has pulmonary tuberculosis Antisyphilitic treatment has been given to the latter, but there has not yet been any significant change in her STS titre The remaining two sero-positive patients were English , one had skin lesions attributed to leprosy and syphilis by different observers, a biopsy showed no evidence of leprosy The last patient was a man of 75 who shows no clinical evidence of syphilis

Earlier work on the occurrence of positive STS in leprosy has been reviewed by Ranque, Tramier, Depieds, and Moignoux (1953) These workers carried out TPI tests on forty leprosy sera (principally from Dakar) and considered fifteen to have given non-specific STS reactions Nelson (1952) examined sera from seventy patients in the Carville leprosarium , 57 were STS-positive, of whom only eleven were reactive with the TPI One of the thirteen STS-negative patients also had a doubtful TPI test Thivolet, Floch, Rolland, and Sohier (1953) examined sera from eighty lepers, mainly from French Guiana fifty were positive with one or more STS, but of these, only twelve were TPI-positive, and one of the thirty STS-negative cases was also TPI-positive Portnoy and Edmundson (1954) in examining 255 leprosy sera found thirty to be reactive with the TPI test, eighteen of these also being reactive with the VDRL slide test Of the 225 sera which were TPI-negative, 65 were reactive with the VDRL test

Haemolytic Anaemia —Although only nine sera were examined from patients with the acquired type of haemolytic anaemia due to auto-antibody production, six of them gave positive reactions with one or more of the STS, while one other had given a bizarre pattern of discordant STS results over the preceding 5 months, but was STS-negative on the specimen on which the TPI was performed The TPI was negative in all cases Despite the small number of cases, it seems probable that non-specific reactions are common in this condition Presumed false-positive Wassermann and Kahn tests were found in two cases described by Dacie (1954) who refers to earlier work

Sera were also examined from seven patients with paroxysmal cold haemoglobinuria In five patients the STS were all positive, usually to a high titre, and these all had a positive TPI test The remaining two patients were sero-negative with the STS and the TPI Dacie (1954), in a tentative classification of this condition, differentiates a chronic type associated with syphilis from acute and chronic types of varying aetiology

Specificity of the STS as judged by the TPI

In the previous comparative results which have been presented the STS have been considered together as a group, representative of tests for reagin(s) in contrast to the test for immobilizing antibody If the results of the latter test are taken as a criterion of the specificity of the STS reactions, the performance of the individual STS can be compared To obviate the influence of antisyphilitic treatment on the tests, treated patients have been excluded and a comparison of results on 572 untreated patients, on whose sera all four STS and the TPI had been carried out on the same specimen, is given in Table X (opposite)

These results show that the order of STS specificity was PPR >Standard WR (crude heart extract antigen)>Kahn>Cardiolipin WR The PPR gave

TABLE X
COMPARISON OF THE INDIVIDUAL STS WITH THE TPI ON SERA FROM 572 PATIENTS

Tests		WR	WR Cardiolipin	Kahn	PPR
Agreement	Both Positive	303	340	304	307
	Both Negative	144	84	120	156
Disagreement	STS 0 TPI+	52	15	51	49
	STS+ TPI 0	73 (13 per cent)	133 (23 per cent)	97 (17 per cent)	60 (10 per cent)

less than half the presumed non-specific results which were found with the more sensitive Cardiolipin Wassermann reaction It should be emphasized that these tests were carried out on a group largely composed of "problem" sera which included a large number of non-specifically reacting sera It is felt, however, that a comparison of individual STS in a group of this type against the TPI as a standard gives a much truer picture of the specificity of individual STS than the more usual procedure of comparative STS testing on large numbers of routine sera in which the incidence of non-specific reactions is very low A similar study on 726 problem sera has been reported by MacPherson, Ledbetter, and Martens (1955) They found the Kahn test to give 39 9 per cent non-specific reactions, the Kolmer 21 4 per cent, and a test using Cardiolipin antigen 29 4 per cent non-specific reactions

A comparison of the individual PPR titres against the TPI result in the same group of sera from 572 untreated patients is given in Table XI

TABLE XI
COMPARISON OF PPR TITRES AND TPI RESULT ON SERA FROM 572 UNTREATED PATIENTS

PPR Titre	Sera	TPI+	TPI 0	
			Number	Per cent *
0	206	50	156	—
Neat	159	132	27	17
2	68	53	15	22
4	46	41	5	11
8	31	25	6	19
16	25	20	5	20
32	17	16	1	6
64 and over	20	19	1	5

*Percentages based on number of sera in each titre group

This shows that while the bulk of the TPI-negative sera which were reactive with the PPR were of low titre (2 dilutions or less), there were small numbers of moderately- or high-titred sera which were considered to be non-specific because of the negative TPI These results are similar to those of Miller and Smith (1953) in a similar study using the quantitative Kahn test, and they suggest that, in general, the more strongly positive the reaction given by the STS, the more likely it is to be specific, particularly where the other STS give concordant results Exceptions to this generalization occur, and some of the highest-titred sera found in the Reference Laboratory have been associated with repeatedly negative TPI tests which have cast doubt on the specificity of the STS concerned In some cases this has been associated with discordance among the STS results, some tests in the battery giving extremely high titres while others are completely negative, and a prozone can be excluded A case of this sort has recently been reported by Wilkinson (1954a)

Discussion

In the evaluation of any serological test it is logical to establish its performance with sera of known antecedents before applying it to the diagnosis of disease This is even more true of a technique which is designed to validate the results given by other tests Examination of presumed non-syphilitic sera has shown that the TPI test has a very high specificity In the small numbers of cases which have been reported where it has given possibly non-specific reactions, the impossibility of proving the negative contention that the patients concerned had *not* got syphilis makes it difficult to arrive at a final conclusion, but the figure of 0 3 per cent possible non-specific reactions given by Zellmann (1954) seems a reasonable estimate

In this study, the use of the TPI as a verification test has been restricted to latent syphilis Complete reliance on it in this role presupposes that it will be positive in all cases of untreated latent syphilis From a consideration of the results in a relatively small number of patients in whom the diagnosis is thought to be well established on other evidence than reactivity of sera with tests using lipoidal antigens, it is clear that the TPI has a very high sensitivity, immobilizing antibody being present in over 99 per cent of the patients studied It should be noted, however, that in three cases doubtful reactions were obtained in untreated patients, this suggests the possibility that spontaneous disappearance of the antibody may rarely occur

Where treatment has been given, it has been assumed as a working hypothesis (Zellmann, 1954) that the behaviour of immobilizing antibody in late latent syphilis (of more than 4 years' duration) is similar to that in late symptomatic syphilis and that it persists indefinitely in almost all cases While this assumption is reasonable, it is often very difficult to

assign an infection to "early" or "late" latency, and this uncertainty will affect the interpretation of a negative TPI test in such cases

The titre of immobilizing antibody is usually high in latency, and reactions in the "doubtful" range are only rarely found, of the 1,126 sera examined in the present study only ten, or 0 9 per cent, gave doubtful reactions

It is considered that the TPI test fulfils the criteria of specificity, high sensitivity, and ability to give clear-cut results which were suggested as essentials for a verification test to be used in suspected latent syphilis A positive reaction is considered to be good evidence of past treponemal infection, but it must be stressed that this is not necessarily an indication of present activity of the disease In untreated patients in whom the only suggestion of syphilis comes from positive STS results, the finding of a negative TPI test, which is confirmed by repetition on a second specimen of serum after an interval of at least a month, is very strong evidence that the STS reactions are non-specific in nature A confirmed negative TPI result in patients who have been treated for supposed latent syphilis on positive STS findings alone suggests non-specificity of the latter tests, but, until more direct evidence of the behaviour of immobilizing antibody in patients treated in known early latency is available, it is felt that judgment should be reserved

Application of the TPI test to sera from blood donors and pregnant women found STS-positive on routine testing has suggested that a significant proportion of these positive reactions are non-specific The observed incidences of 35 per cent and 27 5 per cent presumed non-specific reactions in donor and antenatal sera are probably over-estimates because of the selected nature of the sera Experience with unselected antenatal sera at the Royal Free Hospital suggests that the figure is of the order of 20-per cent While even this latter figure seems disconcertingly large, reflecting discredit on the STS employed, it is important to view it in perspective and to realize that it also means an incidence of only 0 2 per cent non-specific reactions among the total 2,512 sera tested, which is acceptable for a serum test Knowledge of the proportion of positive STS in pregnancy which may be non-specific is, however, of more immediate value to the clinician faced with a pregnant woman whose routine tests have been found to be positive Examination of untreated patients with suspected latent syphilis attending venereal disease clinics has shown that in about one in ten the TPI is negative, suggesting that the STS are non-specific, and that, of those treated in the past, 4 4 per cent are TPI-negative It is felt that these proportions are sufficiently large to emphasize the need for some form of confirmatory test to establish the validity of the STS in these types of patients At present, the TPI, despite its technical difficulty, seems to offer the best approach to the problem Two other verification tests used in recent years, the Kahn verification test and the Neurath euglobulin inhibition test, were compared with the TPI on a small series of sera, but were not thought to give reliable results (Harrell, 1953, Roy, Hill, Gowdey, Kelcec, and Rein, 1953)

While the immobilization test is of great help in the investigation of patients thought to give non-specific STS reactions, it does not answer the fundamental question why some patients, either in apparent good health or suffering from diseases other than syphilis, should give non-specific reactions with serum tests for syphilis Kahn (1950), in his work on the Universal Serological Reaction, suggests that as a result of normal tissue wear and tear, lipoidal substances are produced which give rise to auto-antibodies which react with the lipoids in these antigens These "normal" antibodies may sometimes be strong enough to overflow into the diagnostic zone of the Kahn test and give a positive result Under appropriate test conditions, different serological patterns are produced, and it is thought that not only established non-specific reactors can be recognized, but also normal individuals who are potential non-specific reactors, their precipitation patterns closely approaching the diagnostic zone of the universal reaction, but not encroaching upon it This hypothesis is attractive in its simplicity, but as yet no data have been published on the results given by the TPI test on sera which have shown the non-specific pattern of reaction when examined by Kahn's new technique

An alternative possibility is raised by the work of Lindau and Laurell (1952) These authors subjected normal, Wassermann Reaction-negative sera to paper electrophoresis, and separated protein fractions of varying mobilities by elution of sections of the filter paper They found that the faster part of the γ-globulin fraction gave positive Wassermann and Kahn reactions which were reversed by Neurath's inhibitor They suggest that normal sera contain reagins whose effects are neutralized by an inhibitory substance normally present, and that non-specific STS reactions might be due to an imbalance with a decrease in the inhibitor

The possibly serious prognostic implication of presumed non-specific STS reactions has been suggested by the work of Moore and others (Moore and Mohr, 1952a, b, Moore and Lutz 1955) A

group of patients from a private practice who showed no evidence of syphilis, other than repeatedly positive STS, was kept under observation for long periods On the basis of negative TPI tests, the STS, most of which had been discovered on routine testing, were considered to be non-specific Detailed clinical examinations and laboratory investigations showed that a considerable proportion of these patients had evidence of unsuspected collagen disorders or that the tests showed abnormalities reflecting alterations in the γ-globulins In the most recent survey (Moore and Lutz, 1955) it was found that out of 148 patients examined, ten had proved systemic lupus erythematosus, while 45 had "probable" collagen vascular disease (usually systemic lupus erythematosus)

While this work underlines the need to investigate patients with presumed non-specific reactions, and not simply to dismiss them when the diagnosis of syphilis is thought to be excluded, there are some features which need stressing By no means all patients with systemic lupus erythematosus show non-specific STS reactions, and these may be absent even when the systemic manifestations are very severe Lupus erythematosus is an ill-defined condition and protean in its manifestations (as emphasized in the recent review by Haserick, 1955), and Moore and Lutz only regard the diagnosis as "proved" in a minority of the patients they have studied, but further observation of the patients placed at present in the "probable" category may result in the establishment of a definite diagnosis Moore's patients are drawn from a narrow population group, and further work is needed to show whether his results are applicable to other classes of patients showing the chronic type of non-specific reaction, when it is not associated with any obvious precipitating cause

Summary

(1) Immobilizing antibody has been demonstrated in all save one of 136 patients in whom the diagnosis of latent syphilis was corroborated by other evidence than the STS results alone In view of the specificity of the test, its great sensitivity, and its ability to give clear-cut results, it is thought to be eminently suitable as a verification test in patients with suspected latent syphilis In an untreated patient where the only presumptive evidence of syphilis rests on positive STS results, it is considered that a negative TPI test, confirmed on a second specimen of serum, is good evidence that the STS results are non-specific in nature

(2) The TPI was found to be negative in 11 5 per cent of 200 untreated patients coming to venereal disease clinics with suspected latent syphilis, and in 4 4 per cent of 248 such patients who had been diagnosed and treated for latent syphilis in the past

(3) 35 per cent of problem sera from blood donors, and 27 5 per cent of problem antenatal sera from patients found to be STS-positive on routine testing gave negative TPI tests In an unselected group of antenatal sera about one-fifth of those giving positive STS were TPI-negative Out of 149 patients with diseases other than syphilis who had been found STS-positive on routine testing, 29 per cent gave negative TPI tests

(4) Using the TPI as a criterion of specificity, an analysis is presented of the performance of four representative STS using lipoidal antigens

(5) Recent concepts of the nature and possible significance of non-specific STS reactions are briefly discussed

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THE MALE GONORRHOEA "CARRIER"*

REPORT OF SEVEN CASES

BY

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Introduction

Relatively little attention appears to have been paid to the male gonorrhoea "carrier" (a man with the disease, and capable of transmitting it, but with no symptoms, or with symptoms so slight as to be ignored), although such cases were well known to develop after inadequate sulphonamide treatment There is little evidence that treatment with penicillin, even in small doses, ever produces a carrier state However, since gonorrhoea is apparently becoming a much more innocuous disease in both sexes,† relatively symptomless and asymptomatic male cases may become of importance in its perpetuation

Attention was drawn to this problem by a patient who first attended the Department of Venereal Diseases, General Infirmary, Leeds, in March, 1953 (Case 1) He was subjected to complete examination in order to establish without doubt that he was a gonorrhoea carrier Bacteriological investigations were repeated on several occasions before treatment was given in order to confirm the diagnosis, and to allow for the possible development of symptoms Study of the Department records from the beginning of 1950 revealed five other similar cases, all of whom appeared to be carriers Although the evidence was less complete in some of them than in Case 1, additional confirmatory investigations (such as examination of the prostatic fluid) had sometimes been done even after a bacteriological diagnosis had been made from the urethra or urine A seventh case presented in December, 1953, and was fully investigated (Case 7) No further cases have since been encountered

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† Of the last thirty female cases of gonorrhoea seen in the Department of Venereal Diseases General Infirmary Leeds only eleven had genito urinary symptoms Seven of these had a vaginal discharge alone but in three of them this was revealed only at examination because the women were suspected of being infected (two of these seven had also *Trichomonas vaginalis* vaginitis) only two had urinary symptoms (dysuria and frequency) and they also had a vaginal discharge two presented because of vulvar irritation and one of these also had a vaginal discharge (she had trichomonads as well) One of the patients with a discharge and urinary symptoms also had abdominal pain but no definite clinical evidence of salpingitis was obtained one of those with no genito urinary symptoms had polyarthritis

Clinical Data

The histories of the seven cases have been kept as brief as possible, and only relevant data included No history of any genito-urinary symptoms whatsoever could be obtained in four of the patients, the symptoms of the other three are detailed in the case histories (Cases 5, 6, and 7) All seven denied having received treatment before their investigation

At each visit the meatus was examined after the urethra had been "stripped", but no abnormality was ever found except at one visit in each of Cases 2 and 6 (see case histories) None of them ever showed any clinical evidence of complications of gonorrhoea All other findings are recorded in Table I, which includes every visit of each patient A summary of the diagnostic bacteriological findings is included in the case histories

Techniques

Urethral Scraping—This was obtained by gently scraping the urethral mucous membrane, beyond the fossa navicularis, with a sterilized platinum loop Smears were stained with Gram's stain, and inoculations made on chocolate agar

Urine—This was examined by the standard "two-glass" test In some cases threads in the urine were removed and examined microscopically after staining, in others the urine was centrifuged and the deposit examined microscopically

Prostatic Secretion—The prostate was massaged immediately after the collection of urine The prostatic secretion was examined as a wet film, stained when abnormal, and also inoculated on chocolate agar The urine passed after prostatic massage ("prostatic urine") was centrifuged and the deposit examined microscopically

Bacteriological Diagnosis—Gonorrhoea was diagnosed in smears on the strength of Gram-negative intracellular diplococci morphologically resembling gonococci, in cultures, on the cultural characteristics of subcultures from chocolate agar (the reliability of the technique has been described earlier (Horne, Bittiner, and Buchanan, 1952) and confirmed since), sugar reactions were carried out in Cases 1 and 7

Case Histories

Case 1 (aged 31)—The patient was examined because his wife was found to have a strongly positive gonococcal complement-fixation test whilst under investigation at

another hospital for "lump in the groin" He denied extra-marital intercourse, as also did his wife, who was subsequently found to have gonorrhoea on examination in the Department

Prostatic smear and culture were negative at the first visit (urethral scraping not done) but a month later, after it had been confirmed that the patient's wife had gonorrhoea, further investigation revealed positive smear and culture of the urethral scraping and 4 days later, positive urethral scraping, smear, and culture, positive-stained thread from urine, prostatic culture, and stained prostatic urine deposit Three days later, there was further bacteriological confirmation of gonorrhoea (including sugar reactions on culture from urethral scraping)

Case 2 (aged 42) —The patient had been living with the same consort for 5 years, and was investigated because their two children, aged 4 and 2 years, were found to have gonococcal vulvo-vaginitis (confirmed subsequently in the Department) The patient denied having intercourse with anyone other than consort, as also did she The gonococcus could not be isolated from her At the patient's first visit the meatus was noted to be abnormally moist, but there was no actual urethral discharge The evidence suggested that he infected the children whilst in the carrier state Smear and culture of the urethral scraping, and prostatic smear and culture, were all positive *Trichomonas vaginalis* was also found in the urine and prostatic secretion

Case 3 (aged 25) —The patient came to the Department of his own accord for reassurance with two friends, all of whom had had intercourse with the same consort (not traced) The two friends were both free from infection The patient admitted that he had recently been exposed to additional risks with other women

Stained urinary thread and prostatic smear were positive

He defaulted from observation before test of cure, but it was eventually discovered that he had been living with a consort who was found to have gonorrhoea on examination in the Department

Case 4 (West African, aged 24) —He was investigated because his regular consort had had two recent attacks of gonorrhoea, diagnosed and treated in the Department The evidence strongly suggested that he infected the consort whilst in the carrier state

Prostatic smear and culture were positive (urethral scraping not done) He defaulted before test of cure

Case 5 (aged 41) —He was investigated because his consort was found to have gonorrhoea on examination in the Department He admitted exposure with her about a month previously, and stated that about 3 or 4 days after intercourse he had seen a slight urethral discharge, which had lasted for 2 days and had not recurred There were no other genito-urinary symptoms

Smear and culture of the urethral scraping, and prostatic culture were all positive

Case 6 (aged 26) —The patient came to the Department of his own accord because he suspected that 4 months previously he had infected his wife and another consort with gonorrhoea On questioning he admitted that he had noticed a very slight urethral discharge on several mornings (before micturition) during the few months before reporting He had no other genito urinary symptoms He stated that his wife had been treated for 'V D" at a clinic elsewhere 4 months previously, and his consort had been diagnosed as having gonorrhoea on examination in the Department about that time At the patient's third visit there was a slight mucoid urethral discharge The evidence strongly suggested that he had infected his wife whilst in the carrier state

Urethral smear and culture, and prostatic culture were all positive

Case 7 (aged 26) —He was investigated because his consort had been found in the Department to have gonorrhoea on several occasions during the previous 4 months Because of the ramifications of the case (several people were involved) it was not possible to be certain when he was infected, but it was known that he was first exposed to the risk of infection at least 4 months previously He stated that between 6 and 7 weeks previously he had noticed a thick yellow urethral discharge, associated with dysuria and frequency of micturition, and (on one occasion) haematuria All these symptoms had subsided over a period of 3 weeks, and he denied having received treatment of any type The evidence strongly suggested that he reinfected his consort whilst in the carrier state

Positive smear and culture (including sugar reactions) of the urethral scraping, and positive stained urinary deposit were found

Discussion

Although difficulties are inevitably associated with the interpretation of information supplied by patients with venereal disease, and with the investigations of such patients, there seems little doubt that the seven cases reported here were gonorrhoea "carriers", and that most of them were probably responsible for spreading the disease while they were symptom-free

All seven were symptom-free at the time of investigation four denied ever having had symptoms, two had had symptoms of urethritis, one marked (Case 7) and one slight (Case 5) but in both the symptoms had cleared up spontaneously, and one (Case 6) had had only mild symptoms of urethritis (an occasional intermittent morning discharge), but, so far as can be ascertained, this was not the reason for his reporting In fact, in none of the series were symptoms the reason for the investigations

Despite repeated careful clinical examinations and provocation by various manipulations, no clinical evidence of disease was found at any time in five cases, and only minimal evidence on one occasion in each of two cases (Cases 2 and 6) In

every case the urine was clear, though sometimes containing a few threads or specks The evidence suggested that five of the cases had remained in the carrier state for at least a month (Cases 1, 4, 5, 6, and 7), one of them for at least 6 weeks (Case 1), and one for at least 4 months (Case 6)

Bacteriological Diagnosis—For convenience of discussion salient bacteriological evidence has been summarized in Table II In five of the cases the diagnosis could be made by the discovery of gonococci in stained urethral smears and/or the growth of gonococci from the same material, although in only one was there any actual urethral discharge, this being very slight and mucoid in character In another case the diagnosis could be made by the discovery of gonococci in a stained pus thread from the urine (no urethral scraping was examined), and in another by the growth of gonococci from the prostatic secretion (no urethral scraping was examined, and the stained urinary deposit showed no gonococci) It is possible that in some cases the organism was a *Neisseria* other than the gonococcus (sugar reactions were done in only two cases), but this is not relevant to the clinical implications of the cases

TABLE II

PRINCIPAL BACTERIOLOGICAL DATA (ABSTRACTED FROM TABLE I)

Case No	Urethral Scraping		Urine Stained Thread or Centrifuged Deposit	Prostatic Secretion			Prostatic Urine Stained Deposit
	Smear	Culture		Pus Cells	Smear	Culture	
1	Positive	Positive	(thread) Positive	+	Negative	Positive	Positive
2	Positive	Positive	—	+	Positive	Positive	
3			(thread) Positive	+	Positive	Negative	
4			(deposit) Negative	±	Negative	Positive	
5	Positive	Positive	(thread) Negative	±	Negative	Positive	
6	*Positive	Positive	(deposit) Negative	±		Positive	
7	Negative	Positive	(deposit) Positive	+	Negative	Negative	Negative

*Mucoid urethral discharge
Positive or Negative for gonococci
Pus Cells (leucocytes) + = more than 5 per high power field
± = present but less than 5 per high power field

Significance of Prostatic Cultures—It is of interest that in five cases gonococci were cultured from the prostatic secretion, in three of these gonococci were also seen in stained films of either the prostatic secretion or of the centrifuged deposit of the prostatic urine (presumably containing prostatic secretion) Care must be taken in interpreting this observation, and it may not be justifiable to conclude that the prostate gland was infected in all these cases In four of the five cases with a positive prostatic culture it was known that the urethra was also culturally positive It is possible that, despite the passing of urine, the prostatic material was contaminated by the urethra during its collection

On the other hand, there is complete concordance in the prostatic fluid between the occurrence of gonococci and the pus cell content In Cases 1, 2, and 3, where there were gonococci in stained smears, there were also excess pus cells (more than five per high-power field) In spite of the limited significance that can be attached to the pus cell content of the prostatic fluid as examined by the technique used here (Horne, 1955) this is evidence that prostatic infection, as well as urethral infection, was present in these cases Since neither excess pus cells nor gonococci were seen in stained smears of Cases 4, 5, and 6, the positive prostatic culture may not mean that the prostate was infected

Gonococcal Complement-Fixation Test (GCFT)—In three cases the GCFT was done once only in two of these (Cases 3 and 4) it was negative, and in the other (Case 6) it was doubtful positive In another three cases (2, 5, and 7) the GCFT was strongly positive on at least one occasion In the last (Case 1) it was doubtful positive on three occasions This illustrates the limited value of the GCFT in such cases

Effects of Treatment—Because of various circumstances different amounts of penicillin were given, ranging from 300,000 units of a procaine preparation to 3 6 million units of a combined procaine and crystalline preparation (Table I, overleaf) There is no reason to believe that a carrier should be more resistant to treatment than a symptomatic case, and there was no evidence in this series of cases that the treatment given was inadequate

The period of observation after treatment varied (Table I), but five cases had at least one test of cure which included culture of the prostatic secretion Unfortunately, with the exception of Cases 1 and 7 (who had repeated elaborate tests), examination of the urethral scraping was not done after treatment, since the importance of this was not appreciated at the time However, no evidence has been obtained that any of the patients have since had a clinical relapse, nor is there evidence that they have since been responsible for infecting others

Conclusions—It seems therefore that, in addition to the many patients encountered nowadays with very mild clinical gonorrhoea, there are some men who have a sub-clinical infection in whom the diagnosis can be made only by very careful bacteriological

TABLE I

SUMMARY OF INVESTIGATIONS

Case No	Date	Urethral Scraping: Smear: Pus Cells	Urethral Scraping: Smear: Gono cocci	Urethral Scraping: Culture: Gono cocci	Urine (first glass)*: Naked Eye	Urine (first glass)*: Centrifuged Deposit: Pus Cells	Urine (first glass)*: Centrifuged Deposit: Gono cocci	Urine (first glass)*: Thread: Pus Cells	Urine (first glass)*: Thread: Gono cocci	Prostatic Secretion: Smear: Pus Cells	Prostatic Secretion: Smear: Gono cocci	Prostatic Secretion: Culture: Gono cocci	Prostatic Urine: Centrifuged Deposit: Pus Cells	Prostatic Urine: Centrifuged Deposit: Gono cocci	Gono coccal Complement Fixation Test
1	4 3 53				Clear										Negative
	14 3 53				Clear	Nil				Nil		Negative	Nil		
	11 4 53	±	Positive	Positive	Clear										±
	15 4 53	Nil	Negative	Positive	Clear one thread	Nil			Positive	Nil	Negative	Positive	+	Positive	
	18 4 53	Nil	Negative	Positive‡	Clear one thread	+	Negative			±	Negative	Negative	+	Positive	∓
	Treatment 1 6 mil units combined penicillin (procaine and crystalline salts in the proportion of 3 1)														
	11 5 53	Nil	Negative	Negative	Clear	±	Negative			Nil	Negative	Negative	∓	Negative	Negative
	16 5 53†	Nil	Negative	Negative	Clear	±	Negative			Nil	Negative	Negative	Nil	Negative	
	2 10 53	Nil	Negative	Negative	Clear	±	Negative			Nil	Negative	Negative	∓	Negative	±
2	20 2 53	±	Positive	Positive	Clear	Nil				+ (*Trichomonas vaginalis* +)	Positive	Positive			+
	Treatment 400,000 units combined penicillin (procaine and crystalline salts in the proportion of 3 1)														
	23 2 53				Very slightly hazy	+	Negative (Sperms +) (*Trichomonas vaginalis* nil)								
	24 2 53				Clear few threads	+	Negative (*Trichomonas vaginalis* +)								
	25 2 53				Clear specks	+	Negative			+ (*Trichomonas vaginalis* +)	Negative	Negative			
	Treatment (because of persisting pus in prostatic secretion) 3 2 mil units combined penicillin (procaine and crystalline salts in the proportion of 3 1)														
	2 3 53				Clear few threads					+ (*Trichomonas vaginalis* +)	Negative		Nil		++
	14 3 53				Clear few specks										+
	4 5 53				Clear few specks	± (*Trichomonas vaginalis* +)				∓ (*Trichomonas vaginalis* +)	Negative	Negative	∓ (*Trichomonas vaginalis* +)		
3	24 10 52				Clear, threads			+	Positive	+	Positive	Negative			Negative
	Treatment 400 000 units combined penicillin (procaine and crystalline salts in the proportion of 3 1)														
	31 10 52				Clear one thread			+	Negative						
4	21 9 50				Clear	±	Negative			∓	Negative	Positive			Negative
	Treatment 600 000 units procaine penicillin														+ −
6	8 6 51	+	Positive	Positive	Clear, few specks					∓	Negative	Positive			
	Treatment 300,000 units procaine penicillin														
	11 6 51				Clear one thread			+	Negative						
	25 6 51				Clear one thread							Negative	+		
	9 7 51				Clear one thread			+	Negative						-
	23 7 51				Clear										
	30 7 51				Clear										
	16 4 52				Clear specks	±	Negative			±	Negative	Positive			∓
	19 4 52				Clear few specks										
	25 4 52	+	Positive Mucoid urethral discharge	Positive	Clear, specks										
	Treatment 2 4 mil units combined penicillin (procaine and crystalline salts in the proportion of 3 1)														
	12 5 52				Clear					Nil		Negative	Nil		−
	6 6 52				Clear										
7	19 12 53				Clear					+	Negative	Negative	+	Negative	
	21 12 53	Nil	Negative	Positive‡	Clear few specks	−	Positive			±	Negative	Negative	∓	Negative	
	23 12 53†	Nil	Negative	Negative	Clear	∓	Positive								− −
	Treatment 1 6 mil units combined penicillin (procaine and crystalline salts in the proportion of 3 1)														
	8 1 54	Nil	Negative	Negative	Clear	∓	Negative			Nil	Negative	Negative	Nil	Negative	− −
	12 3 54	Nil	Negative	Negative	Clear	±	Negative			Nil	Negative	Negative	Nil	Negative	

For footnotes see foot of p 159

investigation When such a case is suspected the investigations should include a stained smear and culture of at least one of the following urethral scraping, urinary threads (if present), centrifuged urine deposit, prostatic secretion, and centrifuged prostatic urine deposit The likelihood of success will obviously depend on the standard of techniques used, particularly for culturing the gonococcus In view of the implications usually associated with gonorrhoea, and especially if the patient is symptom-free, more than one positive result should be sought if possible before a diagnosis is made A GCFT should always be done in such cases, but the limitations of this test have been referred to, and it should not be relied on for a diagnosis

The importance of the male "carrier" should not be overrated, but in areas where the incidence of gonorrhoea is increasing, or is considered not to be declining rapidly enough as a result of currently used methods of control, the possibility of male "carriers" contributing to the infectious pool (usually attributed only to females) should be considered

Summary

1 Attention is drawn to the existence of the male gonorrhoea "carrier" (a man with the disease, and capable of transmitting it, but with no symptoms or with symptoms so slight as to be ignored) Seven such cases were encountered in 4 years in a venereal diseases clinic

2 These cases are described, and the clinical and bacteriological evidence supporting the diagnosis is presented The examinations necessary for the investigation of such cases are reviewed

3 The implications of the male gonorrhoea "carrier" are discussed

The cultural and serological investigations were carried out in the Bacteriological Laboratory, School of Medicine, Leeds, under the direction of Professor J W McLeod, and latterly of Professor C L Oakley

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Footnotes to Table I

Urine
*The second glass in the two glass test was clear and free from threads and specks on every occasion
Threads = coiled threads more than a few mm long
Specks = all other smaller particles
Pus Cells (leucocytes)
+ = more than 5 per high power field
± = 5 or less per high power field

Gonococcal Complement fixation Test
± = Doubtful positive
+ = Slightly positive
+– = Strongly positive

†Anterior urethroscopy—normal

‡Sugar reactions—gonococci

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BENZATHINE PENICILLIN IN THE MANAGEMENT OF THE TREPONEMATOSES*†

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INTRODUCTION

Twelve years ago investigators of the Liverpool School of Tropical Medicine (1943) and Lourie and Collier (1943) showed the effectiveness of penicillin in spirochaetosis, and staff members of the United States Public Health Service (Mahoney, Arnold, and Harris, 1943) demonstrated the curative power of this antibiotic in venereal syphilis Experience with penicillin has since accumulated impressively and the decade following the second World War became one of complete reorientation in the management of venereal syphilis and of the non-venereal, endemic treponematoses, highly prevalent in many underdeveloped rural areas of the world

Five years ago I had the privilege of speaking to the Medical Society for the Study of Venereal Diseases on the treponematoses—syphilis, yaws, and pinta—as a world problem The doubts about the *curative effectiveness* of penicillin alone as an anti-syphilitic drug were then perhaps only beginning to be dispelled in Britain, while in many other

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† Presented by invitation to the Medical Society for the Study of Venereal Diseases January 28 1955

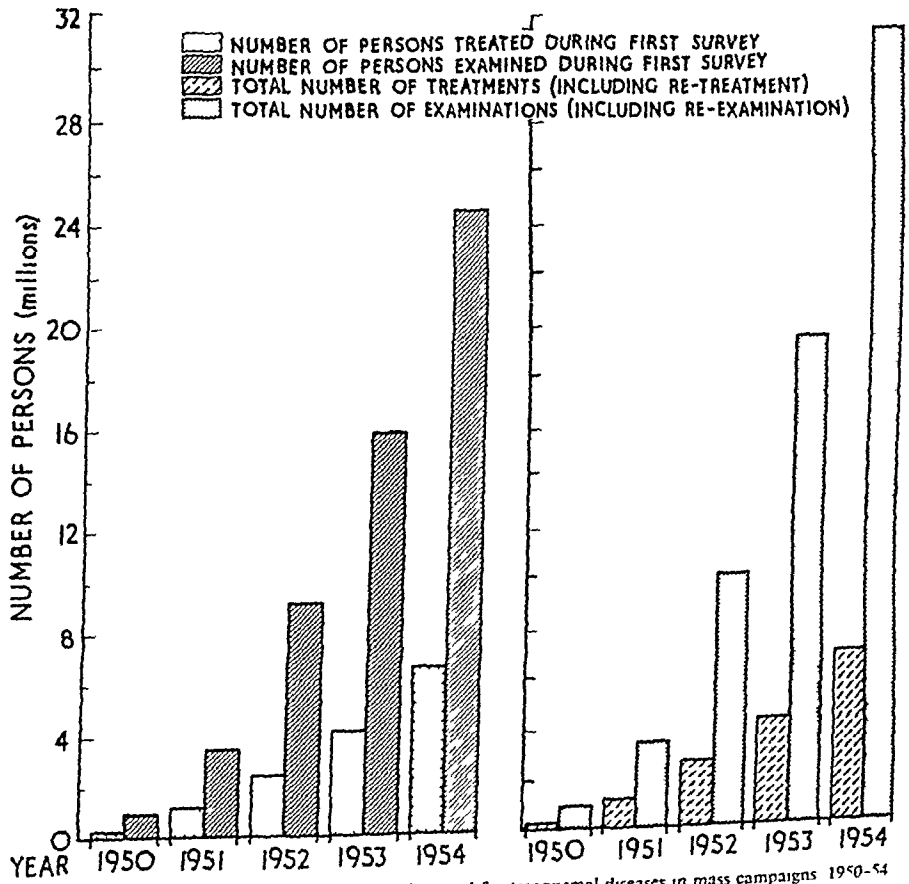


FIG 1.—Total number of persons examined and treated for treponemal diseases in mass campaigns 1950-54

countries medical workers, taking a more traditional attitude, were relying solely on their past experience with metal chemotherapy To-day the outlook has changed practically everywhere, and penicillin alone has become the drug of choice throughout the world This is illustrated by an international study undertaken by WHO in 1953 in which some 70 per cent of 277 leading clinics of dermato-venereology in 55 countries were reported to be using penicillin alone in the treatment of early syphilis (Willcox, Guthe, Idsoe, and Reynolds, 1954) Furthermore, there is increasing evidence that penicillin is gradually being used as the sole treatment for all forms of the disease, including the latent and late systemic stages Another noteworthy trend has been the tendency to draw conclusions on the long-term curative value of penicillin in the treponematoses after a much shorter period than would have been possible in the era of metal chemotherapy According to classical criteria, a patient adequately treated for early syphilis with metals and showing negative blood and cerebrospinal fluid tests after 4 years had every reason to consider himself permanently cured To-day, an increasing number of investigators are prepared to consider a patient cured after only 2 years' observation This attitude is undoubtedly based on the fact that most of the true penicillin failures in the treatment of the early infection occur within 6 to 9 months of treatment and are very seldom observed after 2 years Furthermore, long-term observations have shown that late involvements of the cardiovascular and nervous systems are apparently very rare indeed after penicillin therapy

From the public health point of view penicillin has demonstrated its great value as an inexpensive weapon in combating the endemic treponematoses on a large scale This is particularly true of yaws, which is highly prevalent in the tropics Five years ago internationally aided mass campaigns against the treponematoses were only just beginning, but they have since developed into going concerns (see Figs 1 and 2) and many have become precursors of broad, long-term, health programmes

Finally, on the laboratory side the *Treponema pallidum* immobilization (TPI) technique has become a useful diagnostic tool, and the *T pallidum* agglutination (TPA) test is now being similarly developed It is a paradox that these tests, which are required for much-needed study of the nature of the immunity phenomena, have only become available at a time when the main interest of the clinician is to apply an intensive form of treatment with penicillin, the immediate effect of which is to bring about the destruction of the treponemes regardless of concomitant immunity processes Quantitative standardization of conventional serological tests for the treponematoses has also become possible through the establishment of international cardiolipin and lecithin reference preparations, as well as of

1948	1949	1950	1951	1952	1953	1954
Poland	INDIA I	INDIA I	INDIA I	AFGHANISTAN	AFGHANISTAN	AFGHANISTAN
	Poland	AFGHANISTAN	AFGHANISTAN	EGYPT	CEYLON	CEYLON
	Yugoslavia	*Poland*	EGYPT	CEYLON	BURMA	BURMA
		Yugoslavia	CEYLON	BURMA	ETHIOPIA	ETHIOPIA
		Indonesia	BURMA	ETHIOPIA	INDIA II	INDIA II
		Thailand	*Ecuador* I	IRAN	PAKISTAN I	IRAN
		Iraq	*Haiti*	PAKISTAN I	S ARABIA	PAKISTAN I
		Ecuador I	*Indonesia*	S ARABIA	ROTTERDAM	S ARABIA
		Haiti	*Yugoslavia*	ROTTERDAM	GUATEMALA	ROTTERDAM
			Thailand	GUATEMALA	TAIWAN	GUATEMALA
			Iraq	TAIWAN	*Yugoslavia*	TAIWAN
			Ecuador II	*Yugoslavia*	*Indonesia*	*Yugoslavia*
			Philippines	*Indonesia*	*Haiti*	*Indonesia*
				Haiti	*Thailand*	*Haiti*
				Thailand	*Iraq*	*Thailand*
				Iraq	*Ecuador* II	*Iraq*
				Ecuador II	*Philippines*	*Ecuador* II
				Philippines	*India* III	*Philippines*
				India III	*Paraguay*	*India* III
				Paraguay	*Laos*	*Paraguay*
					Liberia	*Liberia*
					Bechuanaland	*Bechuanaland*
						Syria
						Sarawak
						Nigeria
						Morocco
						Malaya
						Fiji
						St Kitts
						St Vincent
						Grenada

FIG 2.—TREPONEMATOSIS CONTROL PROJECTS ASSISTED BY WHO AND UNICEF 1948–54 Countries printed in small capitals denote demonstration and training projects countries printed in italics denote mass campaigns roman numerals indicate more than one project in the same country

freeze-dried reference sera at different levels of reactivity These are now available at the WHO International Serological Reference Laboratory at the State Serum Institute in Copenhagen, which will distribute them on request to national V D laboratories in many countries At the same time, preliminary information has been accumulating, leading to the definition of certain biochemical characteristics of the treponemes as well as of the influence of certain physical factors in the host environment—particularly in regard to the hyaluronic acid/hyaluronidase system—and the influence of endogenous temperatures in the body on the selective localization of lesions in different tissues and systems These studies, many of which have been carried out at the WHO International Treponematosis Laboratory Center,* suggest new and promising approaches to the ultimate solution of the riddle of the inter-relationship of the treponematoses

PENICILLIN IN THE MANAGEMENT OF THE TREPONEMATOSES

The penicillin preparation which has gradually become accepted in individual and clinical practice as well as in mass campaigns is PAM (procaine penicillin G in oil with 2 per cent aluminium monostearate), introduced by Buckwalter and Dickinson (1948) In spite of its recognized advantages some limitations have been ascribed to this preparation, particularly in individual and clinical practice in the more highly developed countries First, side-effects are apparently more frequent than was previously observed, these are referred to later Secondly, the injection of initial, large " insurance " dosages of 1 2 or 2 4 mega units and " single session " treatments with total doses of 4 8–6 0 mega units have meant injection into several depot sites and have, in the case of large doses, tended to cause local discomfort and complaints of a ' lumpy " feeling Thirdly, PAM has been found to vary in quality, so that the duration of the penicillinaemia—and therefore of the curative effect—may differ not only from one product to another, but also between different batches from one manufacturer This aspect is further complicated by the fact that laboratory experts have been unable to agree on the reliability of suitable standard methods for the assay of penicillin in blood and tissues

The existence on the international market of substandard preparations of PAM led WHO to establish certain minimum requirements in 1950 Steps have recently been taken by the WHO Expert Committee on Biological Standardization to revise these requirements, and an International Reference Preparation of PAM, against which manufacturers will be able to check their products, is envisaged An improved method, using rabbits rather than humans, is also to be developed for the assay of blood concentration resulting from any repository penicillin These developments are the result of cooperation between the United Kingdom and WHO

Penicillin Salts

During recent years the antibiotic properties of a number of new penicillin salts have been investigated Some salts have been under clinical trial for some time, in an attempt to find derivatives which might cause fewer sensitization reactions, for example, the so-called " hypo-allergic " penicillins, such as allylmercaptomethyl penicillin (penicillin O) (Weiss and Wright, 1953) and phenyltoloxamine penicillin (Granatek, Gottstein, and Cheney, 1954) Others have been developed in a search for preparations with repository effect which might obviate the use of procaine or oily components, *e g*, benethamine penicillin, which appears to possess properties very similar to procaine penicillin, and penicillin G diethylamino-ethylester hydriodide (" Neopenil "), which has produced cerebrospinal fluid concentrations ten times as high as other penicillins (Schimmel, Wilson, Matteucci, and Flippin, 1952) The most important development, however, has been the introduction of *N,N'*-dibenzylethylenediamine dipenicillin G, known as benzathine penicillin G,* first described by Szabo and others (1951) Studies of its properties have been carried out by Elias, Price, and Merrion (1951), Lepper, Rodriguez, Blatt, and Spies (1952), Seifter, Glassman, Begany, Ehrich, and Beckfield (1954), and others This procaine-free, slowly absorbed, amino-salt of penicillin G has low toxicity, few side-reactions, and a penicillinaemia of long duration, whether administered orally or intramuscularly In addition, there is the obvious advantage that the oily vehicle used in the repository PAM preparations can be dispensed with in parenteral benzathine preparations

Curative Aspects—A number of reports have been published on the therapeutic use of benzathine penicillin in various infections These are summarized in Table I (opposite), which also shows the considerable interest that exists concerning the treatment of treponematoses, which is demonstrated by the number of clinical trials in syphilis, yaws, and pinta under way in different countries, in many

* Johns Hopkins University School of Hygiene and Public Health Baltimore Md U S A

* Trade names Tardocillin Extencilline Scurocillin Duropenin Penidural Bicillin Capacilina Wycillina and others

instances as part of the activities of an international cooperative group established by WHO

Since "the major determinant factor in the therapeutic activity in penicillin is the aggregate time for which the drug remains at bactericidal levels" (Eagle, Fleischman, and Musselman, 1950), it is of primary interest to compare the penicillinaemia obtainable with benzathine penicillin G with that obtainable with PAM This is illustrated in Fig 3 (overleaf), showing the penicillinaemia curves of the two repository preparations following several schedules Curves are also included for "Panbiotic" or "all-purpose penicillin"—a triple combination of potassium (0 3 mega units), procaine (0 3 mega units), and benzathine penicillin G (0 6 mega units) investigated by Rein, Buckwalter, Mann, Landy, and Flax (1953), and for benzathine penicillin G in oil with aluminium monostearate (BOM)

These are *average* values of units of penicillin per ml serum, as determined by the standard

TABLE I
USE OF BENZATHINE PENICILLIN G IN VARIOUS INFECTIONS

Condition	Benzathine Penicillin G		Author	Date	Patient Series
	Oral (units)	Parenteral (units)			
Mixed pulmonary infections	250 000 and 500 000	—	Lepper and others	1952	32 children
Gonorrhoea	—	300 000 500 000 2 5 mega	O Brien and Smith	1952	396 cases
Rheumatic fever	—	600 000 repeated	Stollerman and Rusoff	1952	135 children
Group B streptococcal infections	(Also peroral indication in some cases)	600 000–1 000 000	Breese	1953	1 204 infections in 793 children
Scarlet fever	7 000 and 13 000 per kg body weight	—	Cornell McAllister Preston and Hunt	1953	38 children of whom eleven had other throat infections
Pneumococcus pneumonia and Group B streptococcus	600 000 initially followed by 300 000 every 8 hours for a minimum of 4 days	—	Finberg and others	1953	63 children
Volunteers	—	600 000	Fletcher and Knappett	1953	19 males
Otitis	—	49 *patients* — 600 000 benzathine penicillin G preceded by or simultaneously with 300 000 procaine penicillin G in one injection 51 *patients* — 600 000 benzathine penicillin G alone	Walker	1954	100 infants and children
Pneumococcus lobar pneumonia	—	(*a*) 1 200 000 (*b*) 600 000	Walker and Hamburger	1954	(*a*) 30 cases (*b*) 19 cases
Pinta	—	Panbiotic 2 4 mega	Marques *Mexico* (quoted by Rein and Mann)	1954	92 cases
Yaws	—	0 6–1 2 mega	Grin and others *Thailand*	1954	236 cases
Yaws	—	Panbiotic 1 2 mega (adults) 0 6 mega (children)	Hill *Jamaica* (quoted by Rein and Mann)	1954	336 cases
Syphilis in adults	—	2 5 mega	Shafer and Smith *U S A*	1954	196 cases
Syphilis in adults	—	2 4–2 5 mega	Smith and others *U S A*	1954	127 cases
Syphilis in adults	—	2 4 mega	Vilanova and Alvarado *Spain*	1954	81 cases
Syphilis	—	Panbiotic 1 2 mega and 2 4 mega	Ribas *U S A* (quoted by Rein and Mann)	1954	132 cases
Syphilis in pregnancy	—	1 2–2 4 mega	Idsoe *Taiwan*	1954*	48 cases
Syphilis in pregnancy	—	2 4 mega	Shafer and Smith *U S A*	1954	8 cases
Early syphilis	—	1 2–2 4 mega	International Co-operative Clinical Group†	—	238 cases

* Communication to WHO
† Barros (*Brazil*) British Clinical Co-operative Group (*U K*) Chaglassian (*Lebanon*) Christiansen (*Iran*) Danbolt (*Norway*), Gay (*Spain*) Hellerström (Sweden) Putkonen (*Finland*) Ragab (*Egypt*) and Rajam (*India*)

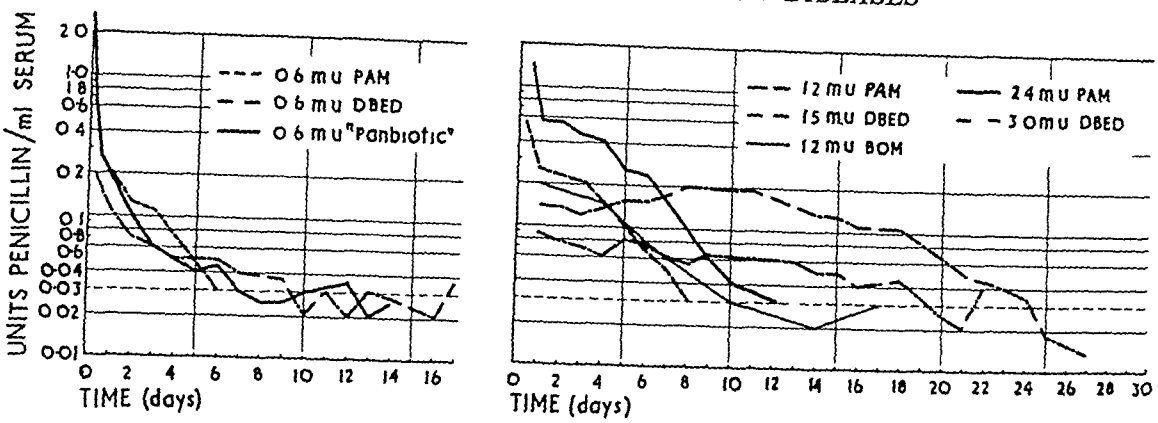


FIG 3 —Duration of penicillinaemia following single injection of PAM, DBED Panbiotic and BOM

Sarcina lutea technique Each curve is based on the findings in at least ten normal ambulant adults Benzathine penicillin G gives a penicillinaemia which has a duration approximately twice that obtainable with PAM (procaine penicillin G in oil with aluminium monostearate) It will be particularly noted that, while 2·4 to 5·0 mega units PAM yield a treponemicidal blood-level above 0·03 units per ml for 11 to 12 days, a very slightly higher dose of benzathine penicillin G maintains this blood-level for more than 22 days One exception will be observed, namely, the curve for 1·5 mega units DBED (benzathine penicillin G, aqueous), which appears to give longer penicillinaemia than 3·5 mega units DBED This curve has been included to demonstrate the influence of weight and the difference in the resulting penicillinaemia in children as compared with that in adults

With regard to "all-purpose penicillin", the main feature is the very high initial concentration of penicillin in the serum, concerning which Schamberg (1953) has stated

> I am wondering whether there is any theoretical basis for feeling that this high early concentration would bring about any better results in syphilis than does the lower blood level provided by Bicillin alone

Some investigators have suggested that the very *low* blood concentrations resulting from benzathine penicillin may be insufficient to kill all treponemes in the infected host This view is not borne out by the evidence furnished by laboratory workers, clinicians, and epidemiologists First, penicillin-sensitive micro-organisms retain and concentrate the antibiotic so that low levels in the environment may result in substantial concentrations in the bacterial cell (Eagle, 1954), treponemes are one of the most penicillin-sensitive micro-organisms known Secondly, the preventive value of benzathine penicillin against infection in the experimental animal as well as in human beings has been satisfactorily demonstrated Thirdly, the clinical and serological results of treatment of actual clinical cases of treponematoses appear to be satisfactory Short-term observations on the therapeutic effectiveness of benzathine penicillin have been made in yaws (Grin, Guthe, Payanandha, D'Mello, and Swaroop, 1954), in pinta (Marquez, quoted by Rein and Mann, 1954), and in syphilis (Vilanova and Alvarado, 1954, and the WHO International Co-operative Clinical Group, of which the British Clinical Co-operative Group is a part) Long-term observations have also been made in the U S A by Smith and his co-workers (1954b) Shafer and Smith (1954) compared the results of treatment schedules of 2·4 mega units benzathine penicillin with those of 4·8 mega units PAM in previously untreated secondary syphilis over a period of two years (Fig 4) Their results show that a dose of 2·4 to 2·5 mega units benzathine penicillin compares favourably with

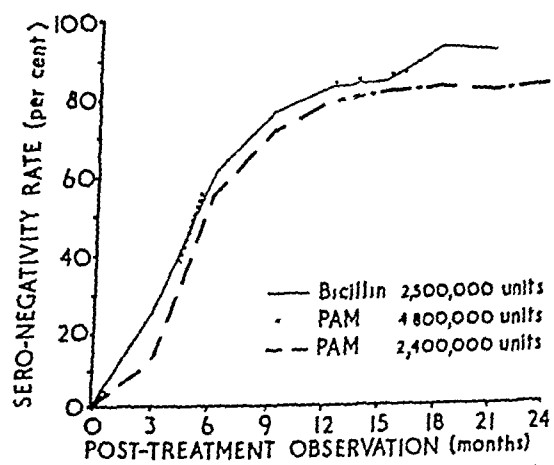


FIG 4 —Comparison of results of bicillin and of PAM in previously untreated secondary syphilis rate of reversal to sero-negativity

one of 4 8 mega units PAM This is to be expected because of the duration of penicillinaemia resulting from benzathine penicillin, since it is not the dosage *per se* or the number of injections which determines the effectiveness of the penicillin, but rather the duration of the exposure of the treponemes to the antibiotic This is determined by the physical, pharmacodynamic, and other characteristics of the penicillin preparation used It is to be regretted that so often in the past the therapeutic effects of penicillin preparations have been expressed only in terms of units and dosages without sufficient regard to the time/exposure factor

The various trials in treponematoses show that benzathine penicillin is a suitable preparation for individual and clinic practice It has simplified the management of syphilis further by permitting single-session therapy to be given with a longer-acting drug in a lesser volume and in an aqueous suspension It is, one might say, the one penicillin preparation so far available which has " time on its side " In mass campaigns in rural under-developed areas the considerations regarding the practical use of benzathine penicillin are, at present, somewhat different The administration of a drug which is not " ready-to-inject ' by medical auxiliaries working under primitive conditions, is not practic-able , moreover, the use of benzathine penicillin requires more supervision and introduces greater problems in handling and sterilization than the " ready-to-inject " PAM Furthermore, although the presuspended aqueous preparations of benza-thine penicillin now available on the international market are suitable for clinical practice, none has so far been demonstrated to be stable under tropical conditions for any length of time It is not likely, therefore, that benzathine penicillin will replace PAM in mass campaigns against the endemic treponematoses until aqueous preparations have been shown capable of withstanding such conditions Certain field studies are however under way, with both aqueous benzathine preparations and benza-thine penicillin in oil with aluminium monostearate The initial results are encouraging

EPIDEMIOLOGICAL INDICATIONS FOR TREATMENT

In communicable-disease control the use of preventive measures on epidemiological indications is well established In addition to treatment of actual cases, prevention may include the isolation of infected individuals to avoid the spread of infection to susceptible contacts, the adoption of short-term measures, such as the administration of protective sera or chemotherapeutic or antibiotic drugs to contacts without sign of disease, or a combination of these and other possible approaches in an effort to safeguard the public health Obviously, consideration must be given to the cost of the method selected, and the relative risks in terms of side-effects must be carefully weighed in relation to the expected seriousness of the acute, chronic, or morbid conditions resulting in the infected individual and population The price to be paid for such protection in terms of serious complications, and sometimes fatalities, is well known with procedures such as vaccination against smallpox, yellow fever, tuberculosis (BCG), and rabies, or following the protective use of sera and gamma globulin

The studies undertaken on the preventive use of drugs during the past few decades, particularly those with antimalarials, are well known, as are experiences with sulphonamide products in infections with staphylococci, meningococci, streptococci, gonococci, certain intestinal pathogens, and other micro-organisms The preventive use of antibiotics in susceptible infections introduced no new principle, but the greater effectiveness, lower toxicity, and fewer complications and side-reactions associated with antibiotic products made possible an extension of the range of preventive medication Thus, for several years penicillin and other antibiotics have been extensively used in prolonged or intensive courses in surgery, to prevent various infections, ranging from those following bowel resection or bone surgery to the management of surface wounds and burns The introduction of repository procaine and benzathine penicillin with long-lasting bacteri-cidal blood-levels has further added to the preventive effectiveness of antibiotics These are also used in ear, nose, and throat infections, and in dentistry where benzathine penicillin is apparently beginning to replace other penicillin salts (Nathanson, Morin, and Mallet 1953)

Macchiavello, Omar, El Sayed, and Rahman (1954) demonstrated the effectiveness of mass penicillin (PAM) prophylaxis among cerebrospinal meningo-coccal meningitis contacts and carriers in the Sudan Pollitzer (1954) has pointed out the impressive preventive effect of streptomycin when given to contacts in endemic plague areas Lyons (1947) used aureomycin protectively in the mass control of trachoma and acute seasonal conjunctivitis in Egypt and Morocco In the U S A Seal and others (1953) showed the preventive effect in strepto-coccal respiratory infections of procaine penicillin and chlortetracycline used over a period of 6 to 8 weeks in a naval population In the United Kingdom similar epidemiological mass-treatment schemes have been used in the prevention of scarlet fever

and sore throat epidemics In combating the recurrence of rheumatic fever, concern is not with a micro-organism already present in the throat of the individual in whom the disease is in the quiescent state, but with the prevention of Group A streptococcal infection Monthly intramuscular injections of benzathine penicillin for 1 year were shown by Stollerman and Rusoff (1952) to be completely effective in preventing this infection in children Karelitz, Chang, and Matthews (1954) showed that procaine penicillin and benzethacil were highly effective in the prevention of bacterial complications of measles The observations of Stollerman and Rusoff have subsequently been confirmed by a number of other investigators Tidwell, 1954, Perry and Gillespie, 1954, Edstrom, 1954, Breese, 1953, Chamovitz and Catanzaro, 1953) In elderly patients with bronchial asthma and pulmonary emphysema, benzathine penicillin is of value in preventing respiratory infections due to haemolytic streptococci, pneumococci, and non-resistant staphylococci (Barach, 1953)

These are selected examples of current preventive uses of penicillin There are many other fields in which this and other antibiotics are now being used, but where the indications are less clearly defined and where the immediate and long-range effectiveness cannot be readily evaluated No doubt there is a certain amount of misuse of antibiotics in most countries to-day, both in curing and in preventing infections Caution in their use should undoubtedly be exercised by the medical profession, and their application should be confined to specific clinical or preventive indications Finland (1953) has stated that, in the evaluation of the preventive use of chemotherapeutic and antibiotic drugs, serious consideration must be given to

(*a*) the price to be paid in side-effects,
(*b*) the best method of accomplishing a set objective,
(*c*) the types of preventive use to which antibiotics should be put

The preventive use of penicillin may thus be classified under two heads

(1) *Short duration, for a specific purpose*, such as *individual* prevention (*e g*, in ophthalmia neonatorum), or *mass* prophylaxis (in meningococcus infection),
(2) *Long or continuous use, e g* aureomycin for endemic trachoma, or penicillin for rheumatic fever

Preventive penicillin treatment may also serve such uses in the management of the treponematoses and WHO has therefore followed with considerable interest the growing practice and the accumulating experience in many countries

Before discussing these aspects, however, it may be useful to record the following definitions

(1) *Prophylactic Treatment* —This concerns susceptible individuals who may become infected with treponemes, *e g*, the prophylactic treatment of susceptible contacts in areas of endemic treponematoses, prophylaxis before venereal exposure, or indirect prophylaxis by the treatment of pregnant syphilitic women before the foetus is infected
(2) *Abortive Treatment* —This concerns individuals in the pre-clinical stage who are proved to be, or suspected of being, infected *e g* contacts in the incubation period in areas of endemic treponematoses, individuals given treatment after venereal exposure, or treating the syphilitic pregnant woman after the fourth month to cure the disease already established in the foetus
(3) *Protective Treatment* —This is also being applied *protectively* in clinical mass campaigns, where it is given to individuals without overt signs of the infection who are really latent cases, but where no laboratory examinations are practicable, and where the aim is to prevent serological and clinical relapses of an already established infection

While a classification of this kind may be highly desirable, it is not always possible to make such distinctions and the term "preventive" (or "epidemiological") treatment is now frequently used to cover all these eventualities

Preventive Treatment in Venereal Syphilis and Gonorrhoea

In venereal syphilis (and gonorrhoea) preventive treatment has its scientific basis largely in the experimental work of Eagle (1949), and Magnuson and Eagle (1945), as confirmed by Levaditi, Penau, Vaisman, and Hagemann (1949) and others The studies of Plotke, Eisenberg, Baker, and Laughlin (1949), Alexander and Schoch (1949), and Alexander, Schoch, and Mantooth (1949) in small series of early syphilis patients and their contacts are well known, as are the views of Leifer and Martin (1946), Durel (1954), and others on the epidemiological effectiveness and applicability of preventive treatment Only passing reference will be made therefore to the work of these investigators as well as to the practical experience of Eagle, Gude, Beckman, Mast, Sapero, and Shindledecker (1948, 1949), Campbell, Dougherty, and Curtis (1949), Babione, Hedgecock, and Ray (1952), and similar unpublished experiences of British workers in the prevention of gonorrhoea or syphilis among naval personnel in ports The evidence suggests that preventive dosages of penicillin in syphilis, or corresponding dosages given therapeutically in gonorrhoea, do not generally "mask" the syphilitic

infection, but apparently prevent it altogether Retardation of the appearance of lesions or the uncovering of the disease by a Herxheimer reaction may occur, but these are extremely rare Recently these observations have been supported by careful investigations (Kolmer, 1954), which indicate that, in the prophylaxis and abortion of syphilitic infection, repository PAM is highly effective, and that benzathine penicillin is almost four times more effective than PAM

This demonstrated effectiveness of preventive penicillin treatment does not mean that the use of this or other antibiotics on epidemiological indication is the accepted practice everywhere There are different views on the subject, not only for venereal syphilis and gonorrhoea but also for the possible risks of syphilitic infection incurred by physicians, dentists, nurses, midwives, and medical technologists in the course of their professional duties Some of these views have recently been published in this journal (King, 1954 , Willcox, 1954) New problems have arisen, ranging from speculation on the ultimate consequences of possible misuse of antibiotics by the profession to the psychological impact which the preventive use of penicillin might have on the public On the latter aspect two opposing views are encountered One is that venereal diseases still strike terror in the hearts of many patients, and that fear and uncertainty about infection are often more catastrophic than infection itself , while the other contends that the ease with which the public now believes that syphilis and gonorrhoea can be prevented and cured with antibiotics has largely removed the fear often associated with these infections in the past There is a growing tendency for the public to regard these infections as they would any other communicable disease

Among the problems posed by the use of penicillin on epidemiological indications is that of the financial responsibility of health insurance and social security organizations Thus, in Germany, the question actually led to an international survey of opinion among venereologists on preventive treatment, with particular reference to married partners, to which McElligott (1953) contributed on the British side Of the twelve participants nine favoured preventive penicillin treatment—some with certain reservations—while three preferred to treat patients after the development of clinical lesions One participant favoured preventive treatment if gonorrhoea was expected, but not if syphilis was the hazard

Other countries have gone further in this question than is perhaps generally recognized , for example, Mexico (Campos Salos, 1952, 1953) and the U S A (personal communication, 1955) In the U S A , health directives now prescribe in detail the procedures to be followed The following quotation is from the Venereal-Disease-Control Manual of Maryland State (1954)

> For some time now it has been customary to treat female contacts of gonorrhoea solely on epidemiological grounds The application of this same principle to alleged sexual contacts of primary and secondary syphilis has been made in several States and in controlled experimental demonstrations There is no doubt that this procedure materially reduces the number of cases of early syphilis developing in the contact group Obviously the advantage lies in
>
> (*a*) the avoidance of symptomatic infection among contacts without clinical evidence of infection who are in the incubation period of the disease at the time of their initial examination, and who would either delay reporting for medical care after the development of infectious lesions or would be completely lost from observation, and
>
> (*b*) a considerable saving in the time required of personnel in the follow up of such contacts
>
> Alleged sexual contacts of primary and secondary syphilis should therefore be treated, following a physical examination and a serological test for syphilis at the time of their initial visit to the clinic If they are found to have clinical syphilis at that visit they will of course receive the same schedule of treatment as would any other case with the same manifestations If, on the other hand, they show no evidence of disease they should be given 1 2 million units benzathine penicillin G (or 2 4 mega units PAM) in a single injection

Although statistical data indicate that the annual incidence of new cases of early syphilis in the U S A as a whole is no higher than that recorded in the Scandinavian countries, penicillin treatment on epidemiological grounds has apparently been accepted as a new weapon in the control of venereal syphilis (and of gonorrhoea) The reason for this is perhaps that small epidemics of venereal syphilis still occur from time to time in the U S A This is shown in Fig 5 (overleaf), which depicts an outbreak of obvious clinical syphilis in Georgia in 1953 (Olansky and Price, 1955)

The relevant observation by the authorities on this remarkable epidemiological episode was as follows

> On this occasion an individual rejected by his draft board was diagnosed as having secondary syphilis As a result of contact tracing and interviewing, approximately seventy cases of primary and secondary syphilis were detected In addition, approximately 200 other patients were treated prophylactically because they had been exposed to syphilis, and enough man-power was not available to apply proper follow-up procedures to these people

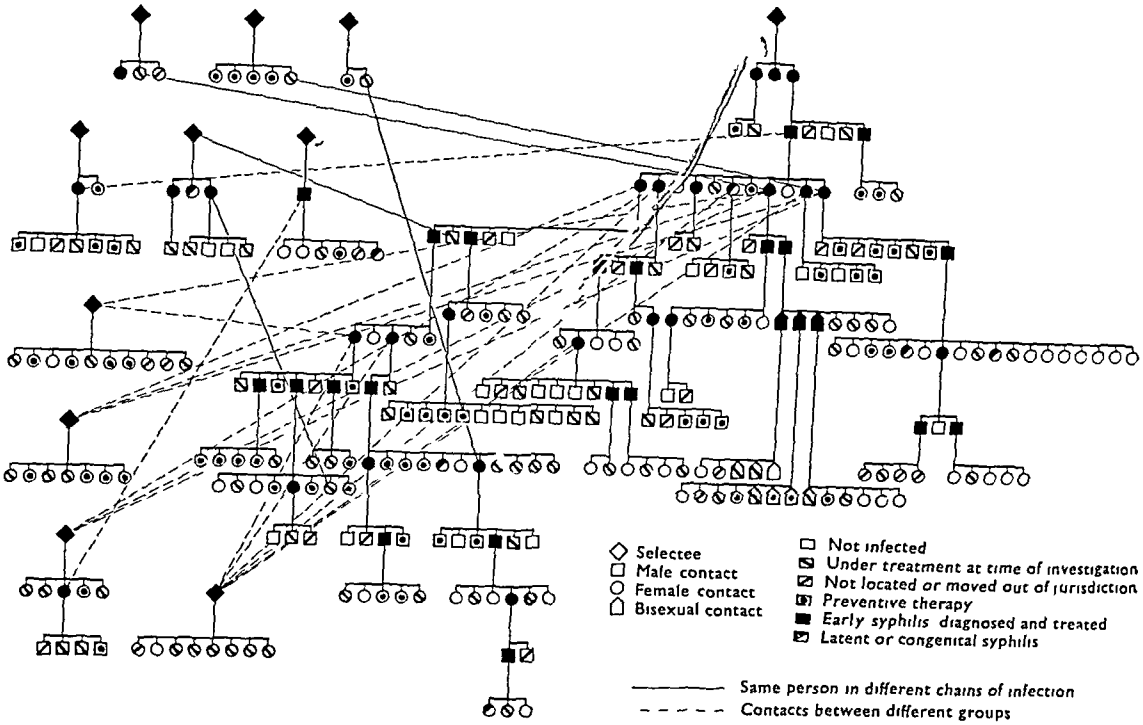


FIG 5 —Schematic diagram of the epidemiology of a secondary syphilis case Troup County, Ga U S A (August 17–October 1 1953) (Olansky)

Contact investigation indexes contact index 4 98 epidemiological index 2 37 brought to R_x index 0 36 lesion to lesion index 0 88

From the references already made concerning the management of venereal diseases in the U S A it is clear that, in that country, the preventive effect of repository penicillin is relied upon to such an extent that it becomes a supplementary arm in epidemiological work At the same time emphasis is being placed on the post-treatment observation of contacts who have received preventive treatment Such contacts should be followed monthly for the first 3 months, quarterly for the remainder of the first year, and annually thereafter

All cases of gonorrhoea are given 0 6 mega unit benzathine penicillin, since this schedule allows adequate time for tracing and treating the regular sexual contacts of the patient, thereby preventing " ping-pong " infections Moreover, it represents adequate treatment for the majority of persons who may be incubating syphilis In the U S A gonorrhoea patients so treated are advised to return 4 months later for a follow-up examination and a serological test for syphilis

In venereal syphilis, Durel (1954) has advocated the use of benzathine penicillin in prostitutes, with appropriate maintenance doses given every 3 to 4 weeks This procedure follows a pattern similar to that previously used in Mexico (Campos Salos, 1952, 1953), Burma, and Hong Kong (reports to WHO), where PAM was given weekly Recently we have had an opportunity of studying in some detail the effect of benzathine penicillin in two female population groups exposed to infection The results are presented in Table II (opposite)

The two groups were living under identical conditions in a walled-off, " red-light ' district of a city, in, let us say, Ruritania The follow up percentages by the end of 12 months observation were 91 and 92 for the test group and the control group, respectively The cumulative attack rate of early clinical syphilis was 13 6 per cent in the control group and appeared to be 3 9 per cent in the test group , this percentage of 3 9 represented one case only—a woman who had missed her previous monthly injection with benzathine penicillin Sero-positivity in the test group showed a declining tendency, although the difference by the end of the first 12 months was not statistically significant However, the trend is suggestive of a ' curative effect in latent syphilis by a regime which by some investigators might be compared to the practice of consolidation treatment

TABLE II

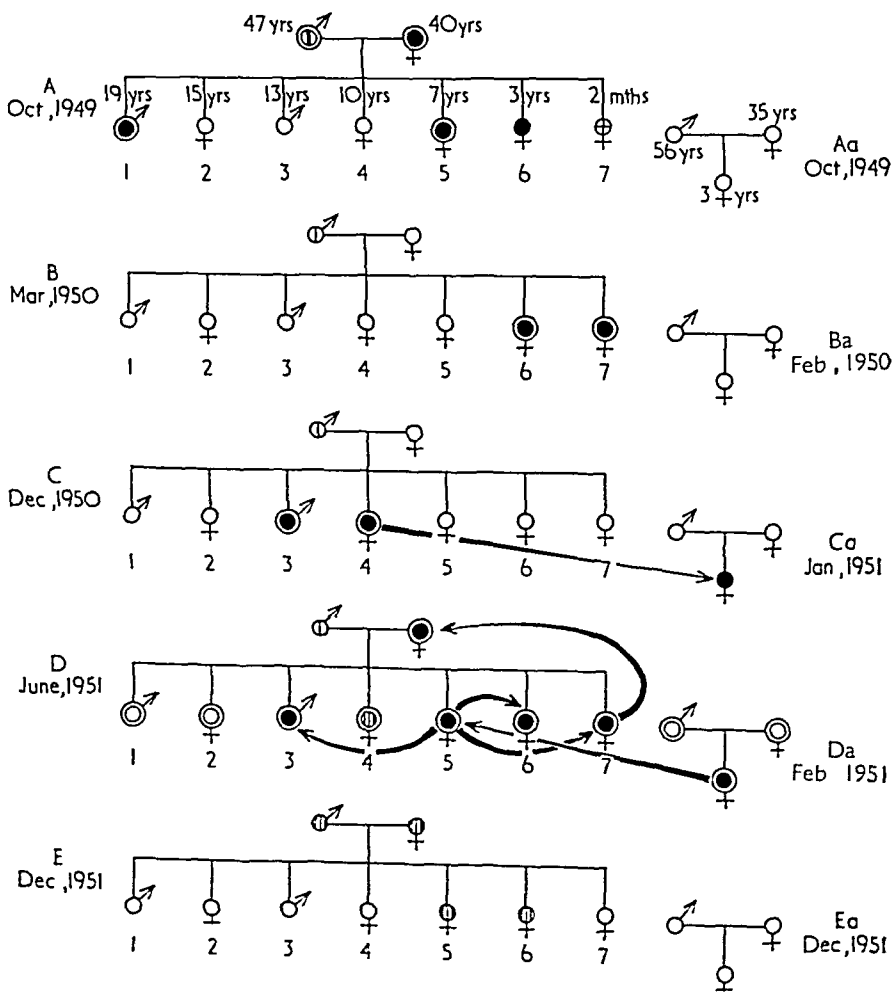
INCIDENCE OF INFECTIOUS SYPHILIS IN EXPOSED FEMALE POPULATION

Number of Months after Beginning of Trial	Test Group (Monthly Maintenance Doses*)						Control Group (Clinical Cases Treated)					
	Number Examined	Sero reactors		Primary Secondary Lesions†			Number Examined	Sero reactors		Primary Secondary Lesions†		
		Number	Per cent	Number	Per cent of Total	Cumulative per cent		Number	Per cent	Number	Per cent of Total	Cumulative per cent
0	32	14	43 7	1	—	—	54	23	42 5	0	—	—
1	31	13	41 9	0	0 0	0 0	53	22	41 5	2	3 8	3 8
2	29	12	41 4	0	0 0	0 0	51	20	39 2	1	2 0	5 8
3	30	12	40 0	0	0 0	0 0	49	19	38 8	0	0 0	5 8
4	28	11	39 3	0	0 0	0 0	51	22	43 1	0	0 0	5 8
5	29	11	37 9	0	0 0	0 0	50	21	42 0	1	2 0	7 8
6	29	10	34 5	0	0 0	0 0	49	20	40 8	0	0 0	7 8
7	30	11	36 7	0	0 0	0 0	50	21	42 0	0	0 0	7 8
8	29	9	31 0	0	0 0	0 0	49	22	44 9	1	2 0	9 8
9	28	8	28 6	0	0 0	0 0	49	21	42 9	0	0 0	9 8
10	27	7	25 9	0	0 0	0 0	50	20	40 0	0	0 0	9 8
11	28	8	28 6	1	3 9	3 9	49	22	44 9	2	4 1	13 9
12	29	6	20 7	0	0 0	3 9	50	22	44 0	0	0 0	13 9

* 2 4 mega units benzathine penicillin G given preventively at monthly medical examinations
† Clinical cases were treated with 4 8 mega units PAM in one session

Preventive Treatment in Non-venereal, Endemic Treponematoses

Penicillin treatment on epidemiological grounds for the mass management of the non-venereal, endemic treponematoses has also received considerable attention in recent years The question has been asked "Is preventive treatment likely to be effective in diminishing the incidence of these infections?" Recent experience may throw some light on this Grin (1953) convincingly demonstrated the effectiveness of preventive treatment in endemic syphilis areas in Bosnia, and he observed that this non-venereal treponematosis, found predominantly in children, was a communicable *household* disease (Fig 6)



- ● Secondary syphilis
- ⊕ Congenital syphilis
- ◐ Latent syphilis
- ○ Clinically and serologically negative
- ◑ Serological improvement
- ◯ Treated (3 600000 units PAM, abortive treatment 1200000 units)

FIG 6 — Ping pong infection and re infection in two infected families and epidemiological effect of abortive treatment (M N O Sapna)

TABLE III

EPIDEMIOLOGICAL EFFECT OF CONTACT TREATMENT IN TREPONEMATOSES MASS CAMPAIGNS

Treatment Policy	Population Examined (Mean)	Percentage Examined of Total Population	Infectious Lesions								Sero reactors							
			Number of Cases				Per 1,000 Population				Number of Reactors				Per 1 000 Population			
			Survey				Survey				Survey*				Survey			
			I	II	III	IV	I	II	III	IV	I	II	III	IV	I	II	III	IV
Clinical cases only	17 526	95 9	1 329	315	82	53	75 8	18 0	4 7	3 0	†	†	†	1,522	†	†	†	86 8
Clinical and serological cases	17,838	96 4	959	42	34	12	53 8	2 4	1 9	0 7	4 823	2 504	1 065	321	270 4	140 4	59 7	18 0
Clinical and serological cases and contacts‡	16 990	97 5	923	8	0	2	54 3	0 5	0 0	0 1	4 715	1 671	611	153	277 5	98 4	36 0	9 0

* Survey intervals 6 to 10 mths
† Not examined
‡ All children under 18 yrs plus members of household with one or more infectious cases

In two households the treatment of clinical and/or serological cases alone did not prevent perpetuation of the disease through cross-infections or re-infections Only simultaneous preventive penicillin treatment of household members without overt signs of the disease, but exposed to the risk of infection, eliminated it These observations were made over a period of 2½ years during which time all household members were clinically and serologically examined and re-examined at five different surveys *Similar observations have been made in other programmes*

The mass effect of preventive penicillin treatment in treponematoses campaigns has also been studied in three endemic areas with approximately the same population, in order to compare different treatment policies (Table III) The basic data and percentage reduction in infections and seropositivity are also shown graphically (Fig 7)

Preventive treatment procedures have been used in many treponematoses programmes, *e g*, the Gold Coast, India, Liberia, Morocco, Nigeria, the Philippines, Thailand, and elsewhere From the experience gained in these campaigns it has become clear that preventive treatment at the initial survey will not only suppress most rapidly and economically the foci of infection in the community, but will also

(*a*) reduce the number of resurveys required to eliminate the infection in rural villages,

(*b*) prolong the interval between resurveys,

(*c*) reduce the overall cost of treponematoses programmes,

(*d*) permit of a more rapid consolidation and the development of a general health programme where treponematoses control has been used as a spearhead

Data on the use of benzathine penicillin G on epidemiological indications in the endemic treponematoses are still limited owing to the present unsuitability of preparations for field use It is nevertheless clear that the longer-lasting treponemicidal blood- and tissue-levels given by this drug will increase the prophylactic value of penicillin in susceptible contacts during mass campaigns, when stable presuspended benzathine penicillin preparations become available there will be more time in the mass programme to suppress active foci from which the infection might again spread in the community The application of such preparations in the incubation period will increase the likelihood of *aborting* completely the treponemal infection, while at the same time providing an extended period of protection against re-infection in exposed

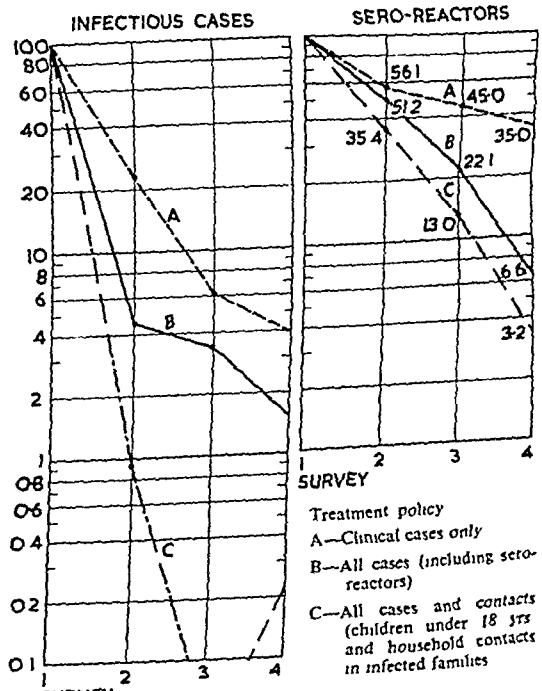


FIG 7.—Infectious cases and sero-reactors of four surveys (undertaken at intervals of 6 to 10 months) according to three different treatment policies

individuals In undiagnosed latency in clinical mass campaigns the prolonged penicillinaemia will tend to provide greater *protection* against relapses

Although the experimental evidence in animals and man suggests the effectiveness of proportionately smaller dosages of penicillin for preventive purposes—and this, for reasons of economy, is the principle currently followed in mass campaigns against the non-venereal treponematoses—the tendency in venereal syphilis appears to be towards the use of relatively large dosages in preventive treatment This trend has developed simultaneously with the tendency

(*a*) to increase the penicillin *dosage* in gonorrhoea to ensure that adequate therapy is provided for a syphilitic infection in the incubation period at the time of treatment,

(*b*) to increase the penicillin *effect* through the use of appropriate dosages of longer-acting preparations such as benzathine penicillin G

In the foregoing discussion, reference has, in general, been made to the *intramuscular* use of penicillin, except for a brief reference to the use of oral tablets among naval personnel in ports Several years ago the WHO Expert Committee on Venereal Infections and Treponematoses warned against the uncertainties and dangers of penicillin tablet medication in gonorrhoea and the treponematoses, and this view now appears to be generally accepted

Side-effects of Penicillin

Turning now to an appraisal of the side-effects resulting from the use of penicillin in the management of the treponematoses, the Jarisch-Herxheimer reaction in infected individuals and the possible development of penicillin resistance in the treponeme are only mentioned in passing, since the lysis phenomenon is a fairly constant feature with any kind of effective antisyphilitic drug and since resistance has not so far proved of practical importance

Of the greatest importance, however, is the risk of sensitization of the host, of which many drugs are capable Untoward reactions might therefore be expected with antibiotics as well Since reactions may be expected to become more frequent as an increasing segment of the population has an opportunity to become sensitized from repeated exposure, it is noteworthy that the oldest and most widely used antibiotic—penicillin—has been scrutinized in this light only during the past few years But it is now well established that penicillin may cause serum-sickness-like reactions (delayed urticaria, dermatographia, angioneurotic oedema, etc, or fixed skin eruptions (contact dermatitis) exfoliative dermatitis, etc) These reactions are usually controlled with antihistaminic drugs On the other hand there are the more important acute, anaphylactic reactions, profound, dangerous, and sometimes immediately fatal, which may follow oral and parenteral administration, or as a result of inhalation or instillation

Sensitization reactions presuppose the presence of penicillin antibodies in the fluids and tissues of the host Although the existence of such antibodies has so far not been demonstrated, studies are proceeding at the International Treponematosis Laboratory Center, where the application of new techniques developed by Dr Ovary of Rome may make it possible to detect very small amounts of antibody This approach may provide a new tool for the study of the entire problem of penicillin sensitization and the nature of antibodies formed in response to antibiotics

The first fatal penicillin reaction was reported by Waldbott (1949) and others have since been published in England, France, and the U S A (Stroud, 1952, Mayer and others, 1953, Siegal, Steinhardt, and Gerber, 1953) In an incomplete survey in the U S A in 1953, the Food and Drug Administration found nineteen fatalities among 59 reactors to penicillin over a period of 2 years in 95 major American hospitals, representing 51,000 hospital beds (Welch, Lewis, Kerlan, and Putnam, 1953) One fatal case was from oral benzathine penicillin G Since then many studies have been carried out by a number of investigators (O'Brien and Smith, 1952, Nathanson and others, 1953, Lepper and others, 1952, Feinberg, Feinberg, and Moran, 1953, Smith and others, 1954b) Reports of more than 150 anaphylactoid reactions from all types of penicillin have now been published In view of this, the frequency and severity of reactions to be expected in the management of the treponematoses have become of major interest to the treponematologist and the venereologist

Kitchen, Rein, Thomas, and Spoor (1951) reported that of 2,106 hospitalized syphilis patients, 4 per cent were reactors to penicillin No severe reactions or fatalities were observed among them Jimenez Quiros (1952) reported 4 5 per cent reactions in syphilitic patients in Costa Rica, and Welch and others (1953) that many of the severe reactions followed procaine penicillin, but made no mention of any fatalities among the syphilitic patients Apart from two cases of anaphylactoid reactions reported by Smith and others (1954b), surprisingly few severe anaphylactoid reactions have been reported in gonorrhoea or

treponematoses patients in spite of the fact that, in 10 years, millions of people have been given penicillin

O'Brien and Smith (1952) reported transient dermatitis medicamentosa in 0 3 per cent of 1,377 patients treated for syphilis with benzathine penicillin G, and Shafer and Smith (1954) found a similar percentage of reactors However, perhaps the most complete analysis of penicillin reactions is that reported in an unpublished study presented at a recent Symposium on Antibiotics in Washington, D C In this material reactions were classified as urticarial and serum-sickness-like reactions, and as anaphylactoid and "other" reactions Between 1946 and 1950 in 185,577 patients at 36 V D centres participating in the United States Public Health Service V D programme there were three penicillin reactions per 1,000 patients with a fatality rate of 1 100,000 (Smith and others, 1954a) This contrasts sharply with the mortality of 1 200 with arsenicals given by intravenous drip and 1 9,000 resulting from neoarsphenamine therapy In 1954 another survey was undertaken in 24 "preventive and control centres" in fourteen States in the U S A , and side-effects were studied in 16,345 patients treated with penicillin during a 3 months' period The outcome of this investigation is presented in Table IV

The following points are of interest

(1) The total reactors averaged 6 67 per 1,000 and among them urticaria was the most frequent reaction, namely, 5 5 per 1,000 Four anaphylactoid reactions occurred 1 1,000, with no deaths

(2) The frequency of reactors increased with the duration of the planned schedule and was lowest (2 to 3 per 1 000) in therapy schedules given in single sessions, and highest (23 to 60 per 1,000) in therapy schedules lasting 2 weeks or more The frequency of reactors to PAM and to benzathine penicillin on a "one session" basis were almost identical (2 to 3 per 1,000)

(3) The frequency of reactors also increased with increasing age—and therefore presumably with increasing penicillin experience—from an average of 3 per 1,000 in the age group 10 to 19 years to 18 per 1,000 in the age group 40 to 49 years Additional effect was observed with increased duration of treatment schedules in the parallel age groups, with nineteen and 81 reactors per 1,000, respectively

(4) Among persons who had no reaction to previous penicillin only 4 7 per 1,000 showed side effects from subsequent penicillin, while 9 5 per 1,000 treated with penicillin for the first time reacted to it However, 101 per 1,000 of those who had reacted to previous penicillin also reacted to subsequent penicillin therapy

(5) The highest incidence of reactions was found in the group treated for syphilis, including those given single-session therapy, where the incidence was 9 9 per 1,000, compared with 2 4 and 2 1 per 1,000 among those receiving gonorrhoea and epidemiological treatment, respectively The dosage in syphilotherapy was eight times that of gonorrhoea and contact treatment This might account for the greater incidence of reactions, although it cannot be ignored that this group may include some Herxheimer reactions, which are recognized as being extremely difficult to differentiate from sensitization reactions

The small chance that sensitizing reactions will occur in children and young people, or in populations with no previous penicillin experience,

TABLE IV

INCIDENCE OF REACTIONS IN 16 345 PERSONS TREATED WITH PENICILLIN
U S Public Health Service—April 15 to August 15, 1954

Treatment Schedules	Total			Single session			2–7 Days			8–14 Days			Over 2 Weeks		
	Total Cases	Reactors		Total Cases	Reactors		Total Cases	Reactors		Total Cases	Reactors		Total Cases	Reactors	
		No	Rate*		No	Rate*		No	Rate*		No	Rate*		No	Rate*
Epidemiological treatment	2 903	7	2 41	2 889	6	2 08	13	1	76 92	1	—	0 00	—	—	—
Gonorrhoea	9 840	27	2 74	9 691	25	2 58	144	2	13 89	5	—	0 00	—	—	—
Syphilis	3 337	75	22 48	1 888	13	6 89	350	11	31 43	637	25	39 25	462	26	56 28
PAM	12 179	97	7 96	10 529	35	3 32	669	14	20 93	587	24	40 89	394	24	60 91
Benzathine penicillin G	3 944	10	2 54	3 856	9	2 33	23	—	0 00	23	—	0 00	42	1	23 81
Age (yrs)															
10–19	3 484	11	3 16	3 253	8	2 46	128	1	7 81	52	1	19 23	51	1	19 61
20–29	7 747	34	4 39	7 151	12	1 68	276	5	18 12	204	10	49 02	116	7	60 34
30–39	2 906	32	11 01	2 479	16	6 45	162	3	18 52	174	6	34 48	91	7	76 92
40–49	1 105	20	18 10	861	6	6 97	74	4	54 05	96	4	41 67	74	6	81 08
50 and over	970	11	11 34	699	2	2 86	49	1	20 41	99	3	30 30	123	5	40 65
Previous penicillin															
Reacted	109	11	100 92	90	7	77 78	10	—	0 00	6	3	500 00	3	1	333 33
Did not react	11 497	54	4 70	10 419	23	2 21	459	6	13 07	370	13	35 14	249	12	48 19
No previous penicillin	3 353	32	9 54	2,770	7	2 53	182	6	32 97	237	7	29 54	164	12	73 17

* Per 1 000

confirms the observations made in mass treponematoses campaigns in underdeveloped areas (Haiti, Indonesia, Thailand, etc) where a surprisingly small number of reactors has been observed Parenteral penicillin is more likely to cause anaphylactoid reactions than oral penicillin, although reactions after the latter have also been reported Persons with hay fever, asthma, or other allergies, or previous sensitivity to penicillin, are more likely to be anaphylactoid reactors Anaphylactoid fatalities are preventable, and care should be taken to avoid accidental intravenous administration of penicillin Calcium gluconate and resuscitation drugs should be ready for immediate use, the preliminary use of skin testing has been stated to be helpful in many instances and procaine amide may be effective in preventing penicillin reactions in known reactors (Jennings and Olansky, 1954)

It is not likely that the use of one penicillin salt will prevent sensitization reactions after the use of other penicillin salts, at least not for those at present in use, including benzathine penicillin

Serious side-effects are not more prevalent with benzathine penicillin than with PAM in single-session treatment schedules in the treponematoses However, subjective complaints of local discomfort at the site of the injection are sometimes made after benzathine penicillin, but such complaints were not considered an objective criterion of "side-reactions" in the study material from the U S A discussed in Table IV That the procaine-free benzathine penicillin may actually give rise to local pain more frequently than PAM is suggested by observations in Thailand (Grin, 1953), Morocco, Norway, and Britain (communications to WHO), although there may be doubts whether this can be considered a contraindication to the use of this preparation if its advantages are otherwise convincing

On the whole, it may be said that the sensitizing potential of penicillin is remarkably low, and while the incidence of penicillin reactions has probably increased in some countries where the drug has been available for some time and has been widely used, reactions remain relatively infrequent considering the enormous quantity of penicillin consumed annually (estimated world production in 1954, 500 tons) Considerable reservation should be made on the general validity of published observations of the stated frequency of penicillin reactions in small, highly selected population samples, such as groups of hospital patients, etc, for material of this kind tends to over-emphasize the true incidence In the long run the use of benzathine penicillin represents an advantage over PAM The use of single-session treatment schedules with benzathine penicillin and the lower dosages which can be effectively administered will tend to limit the degree of sensitization and the number of penicillin reactors A practical consequence of this has been that in the U S A the manufacture of PAM is now being discontinued in favour of benzathine penicillin

SUMMARY

No small proportion of the world s penicillin production is used in the management of the treponematoses The long-acting characteristics of procaine penicillin G in oil with 2 per cent aluminium monostearate—PAM—have, during the past few years, made it the penicillin preparation of choice, since the major factor in the effectiveness of penicillin is the time for which it maintains a treponemicidal level in the blood The recent introduction of benzathine penicillin G—which, when given intramuscularly, is absorbed and eliminated about twice as slowly as PAM—therefore represents a considerable advance in the further simplification of the management of treponemal infections

Clinical trials have shown that the same curative effect can be obtained in early treponemal infections with a single injection procedure using a dosage of benzathine penicillin half that of PAM

Preventive treatment on epidemiological indications is an established principle in the effective management of the non-venereal, endemic treponematoses In some countries such procedures have also been introduced in the management of venereal syphilis (and gonorrhoea) The superior preventive effect of benzathine penicillin (as compared with PAM) has been demonstrated in individuals exposed to contagion and in individuals incubating the treponematoses

The sensitizing potential of penicillin is low, but previous experience with the antibiotic, repeated application in prolonged treatment schedules, and possibly the use of large dosages, tends to increase the incidence of reactions The price to be paid in side-reactions from penicillin is small in relation to its curative and preventive value, particularly when compared to the toxic reactions and mortality resulting from arsenotherapy The introduction of benzathine penicillin in the management of the treponematoses will further limit the incidence of sensitization reactions, since lower dosages make one-session treatment schedules a practical proposition

The data available on the place of benzathine penicillin in the management of the treponematoses

are still incomplete and more time must elapse before a fuller evaluation of its advantages and disadvantages can be made However, in some countries, benzathine penicillin G is already replacing PAM in clinical practice in the management of syphilis (and gonorrhoea) It is suggested that when more stable presuspended preparations become available benzathine penicillin might become the preparation of choice in the control of the non-venereal, endemic treponematoses

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PERIPHERAL NEURITIS ASSOCIATED WITH A PULMONARY LESION IN A PATIENT WITH SYPHILIS*

BY

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The present interest in the association of peripheral neuritis with bronchial carcinoma prompts us to record a case in which peripheral neuritis accompanied a pulmonary lesion presumed to be of syphilitic origin

Case Report

A married bricklayer, aged 56 years, attended a venereal diseases clinic on April 29, 1954, complaining of ill health of 12 months' duration which he attributed to syphilis Why he was so certain of the diagnosis was not disclosed There was no history of early syphilis or any other venereal infection, extra-marital coitus was denied, and there had been no marital coitus for 14 years This last statement was confirmed by his wife His previous health had been good

History of Present Illness —There had been a general increase of malaise and weakness, with anorexia, loss of weight, and occasional attacks of vomiting, not related to any particular article of diet, which occurred during meals He did not complain of any chest symptoms, but on questioning admitted to having had a cough for some considerable time, though he could not remember if this had preceded the other symptoms He began to have difficulty in walking 14 days before admission There was no history of any febrile attacks, haemoptysis, pains, or paraesthesia, and he had had no treatment of any kind He was a heavy cigarette smoker and drank alcohol in moderation, and, as far as could be ascertained, there were no industrial hazards to which the illness could be attributed

Clinical Examination —He was ill and anxious-looking and had obviously lost weight He walked with a stoppage gait and was dyspnoeic on slight exertion No vomiting attacks occurred during his stay in hospital The cough was loose and frequent with about 5 oz mucopurulent sputum daily There was no genital scarring or other signs suggestive of syphilis on the skin or mucous membranes Examination revealed an area of consolidation in the upper lobe of the right lung The heart appeared normal, the systolic blood pressure was 150 mm , and the diastolic 75 mm Hg No abnormality was detected in the abdomen The cranial nerves were intact The superficial and tendon reflexes including the knee and ankle jerks were normal There was no loss of power in the upper limbs, trunk, or thighs The muscles supplied by the common peroneal nerves were paralysed with consequent foot drop and flexion of the toes Palpation along the nerves in their superficial course revealed no thickening or other abnormality A number of observers verify that the sensory divisions of these nerves were intact He was afebrile and weighed 144 lb

Investigations

Radiology —*X*-ray of chest (Fig 1) shows an area of consolidation in the anterior and postero-lateral segments of the upper lobe of the right lung

Fig 1 —*X* ray of patient April 29 1954 showing area of consolidation in anterior and postero lateral segments of upper lobe of right lung

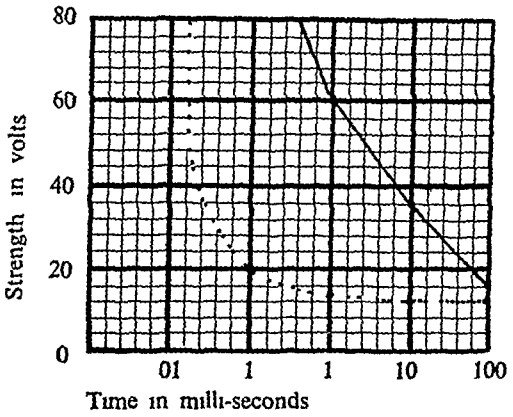
Bronchoscopy (Mr Victor Brookes) —No abnormality present

Sputum —Repeatedly negative for *Mycobacterium tuberculosis* and malignant cells

Blood —Haemoglobin 11 8 g (80 per cent) Total white cell count 11,000 per ml Differential count neutrophil polymorphs 75 per cent , lymphocytes 22 per cent , eosinophils 0 5 per cent , monocytes 2 per cent Erythrocyte sedimentation rate 85 mm

Serum Tests for Syphilis —Wassermann reaction and Kahn test repeatedly positive Quantitative Wassermann titre 1 160

* Received for publication November 9 1954



——— Denervated muscle
--- - Normal muscle

Fig 2.—Strength duration curve (control)

Cerebrospinal Fluid.—Wassermann reaction (Harrison-Wyler) complete inhibition of haemolysis in 2 vols of cerebrospinal fluid, partial inhibition in 1 vol, complete haemolysis in remaining dilutions

Urine.—Albumen a trace, 2 polymorphs, scanty red cells, and a fair number of granular casts per high-power field

Electrical Reaction of Muscles (Figs 2 and 3).—These were greatly delayed

Treatment.—30 gr Potassium iodide three times daily and 8,750,000 units crystalline penicillin were given

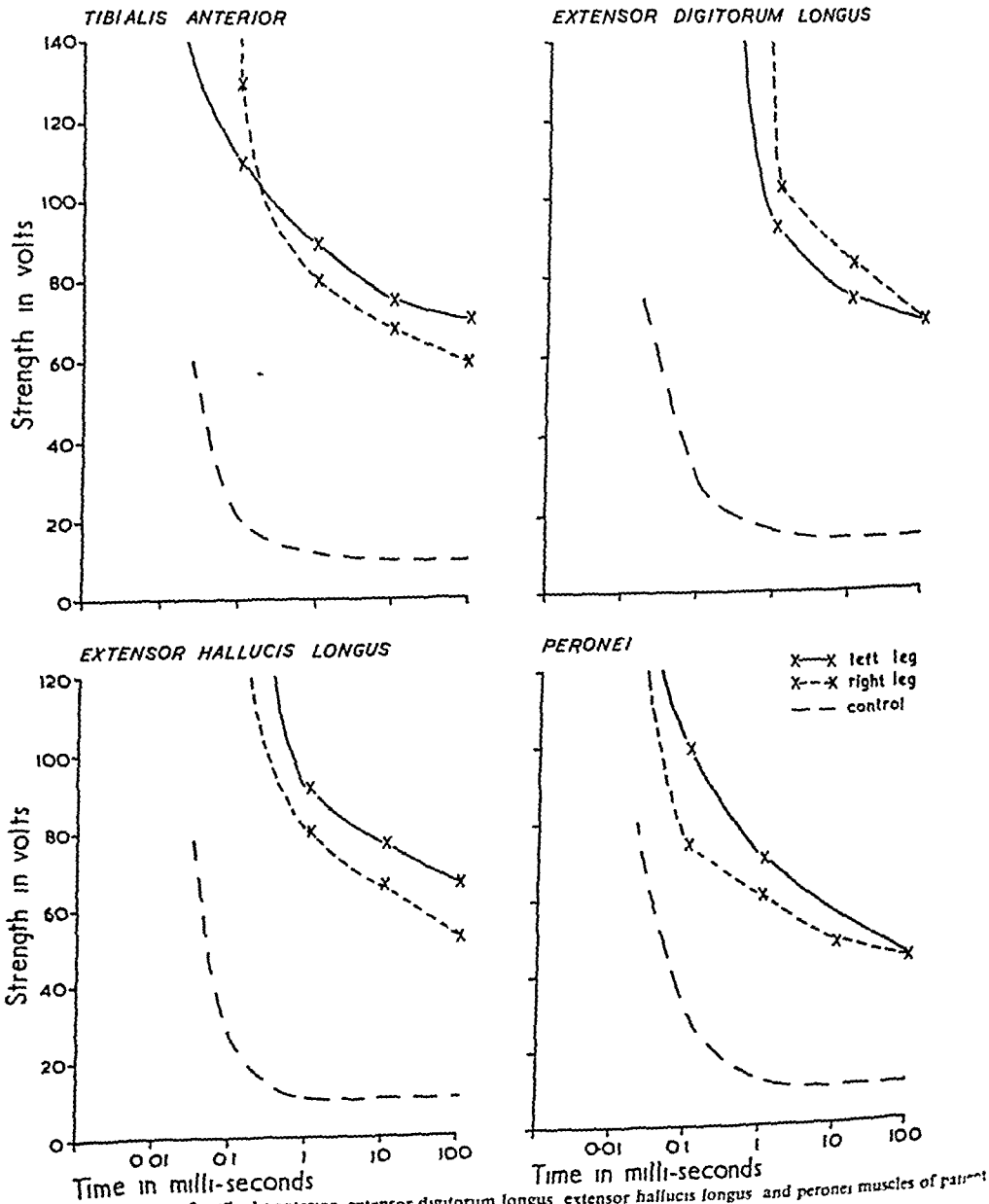


Fig 3.—Strength duration curves for tibialis anterior extensor digitorum longus extensor hallucis longus and peronei muscles of patient

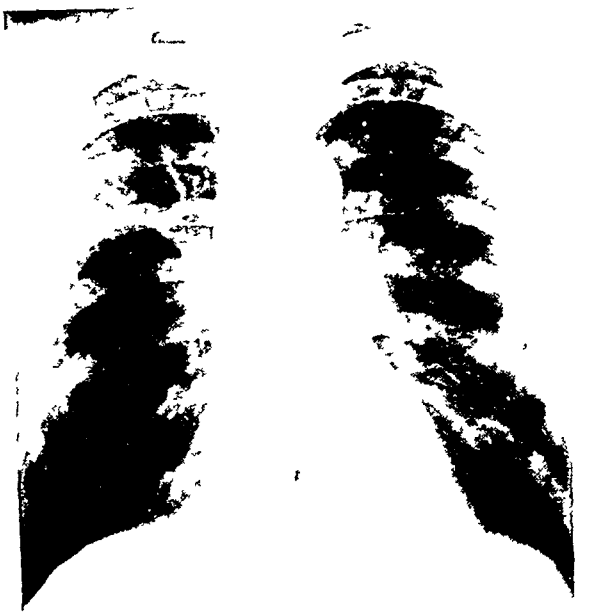


Fig 4 — X ray of patient July 17 1954 showing residual shadowing and slight elevation of upper horizontal fissure

between May 8 and 26, 1954, followed by 1 2 g N A B and 6 ml Bismostab (1 2 g metallic bismuth)

Progress —Towards the end of the second week of therapy the cough became less troublesome, the amount of sputum was greatly diminished, the abnormal lung signs were less pronounced, and the urine became normal Subsequently the lung lesion steadily improved Radiologically the shadow was appreciably smaller on May 25, 1954 , on June 16 the lung was almost clear , and on July 17 there was only residual shadowing and slight elevation of the superior horizontal fissure (Fig 4) The general symptoms disappeared as the lung healed, the appetite returned gradually, and he began to put on weight The erythrocyte sedimentation rate was 57 mm on June 2, 28 mm on June 28, and did not return to normal until August 17 On this date he weighed 154 lb , an increase of 10 lb The quantitative Wassermann reaction was positive in a titre of 1 80 on August 17, 1954, and was unchanged on September 21, 1954, when Price s precipitation reaction (in a titre of 1 32) and treponemal immobilization test were also positive The signs of peripheral neuritis remained unchanged until 7 weeks after the commencement of therapy when power began to return to the affected muscles Complete function was not restored until September 16, 1954

Discussion

Syphilis of the lung is an uncommon pulmonary condition and presents no distinctive clinical or radiological features (Perry, 1952) In the absence of histological evidence, only a tentative diagnosis based upon the exclusion of commoner pulmonary conditions, particularly neoplasm and tuberculosis, is possible A history of syphilis and unequivocal signs of this infection elsewhere in the body, positive serum tests, and response to antispecific therapy are additional guides to diagnosis (Hartung and Freedman, 1932) Similarly peripheral neuritis is rare in syphilis and may be indistinguishable clinically from that due to other causes (Hobhouse, 1945), although apparently at times the affected nerves may be thickened or show nodular swellings (Nonne, 1916)

The criteria for clinical diagnosis are similar to those for pulmonary syphilis namely, positive anamnesis, absence of other aetiological factors, and a response to antisyphilitic therapy (Nonne, 1916)

In the present case there were no definite clinical signs of syphilis and no previous history, although the patient's choice of clinic might throw doubt on this However, the persistence of high titre positive serum tests for syphilis almost 5 months after treatment had been started and 3 months after the lung lesion had healed suggests that the reactions were specific and not biologic false positives, as the latter tend to revert quickly to negative with cure of the infection responsible for their production The positive TPI test confirms that the patient did in fact have syphilis

There is nothing in the history of this case to suggest an independent aetiology for the peripheral neuritis, and the response to therapy suggests that there was some relationship between the pulmonary and nerve lesions The response to therapy also showed that the pulmonary lesion was neither neoplasm, particularly of the bronchus, in which the incidence of peripheral neuritis is about 2 per cent (Lennox and Prichard, 1950), nor tuberculosis, in which peripheral neuritis occasionally occurs (Wingfield, 1929) and makes peri-arteritis nodosa, a possible cause of the combined lesions, extremely unlikely The rapidity with which the lung healed also makes a mycotic infection impossible Though a coccal or viral origin for the pulmonary lesion cannot be eliminated with certainty, the long duration of the illness and the absence of any febrile episodes make either unlikely We do not consider it unreasonable to assume that the pulmonary lesion was chronic because otherwise it is difficult to account for the ill health of a year's duration Had treatment been initiated with metallic bismuth, it might have been possible to eliminate both these possible causes with certainty Penicillin has too wide a range of activity to be of value as a therapeutic test , it was not given for this purpose, but to control the specific infection quickly so that the patient might be more able to

cope with the more strenuous treatment which at that time it seemed probable he would have to undergo

We therefore believe that a diagnosis of pulmonary syphilis is justifiable From the rapidity with which the lung recovered and the completeness of this recovery it would appear that the lesion was an early one and probably confined to gummatous infiltration of the blood vessels of the peribronchial and alveolar tissues (Pearson and de Navasquez, 1938)

Having decided that the patient had syphilis and that this was probably responsible for the lung lesion, it remained to be seen if the peripheral neuritis could also be ascribed to the specific infection This cannot be determined with any certainty, but the time at which the neuritis appeared and the slow recovery incline us to the opinion that the nerve lesion was not due to the specific infection but to a factor as yet unknown which causes peripheral neuritis in the late stages of some chronic infections, for example, bacillary dysentery, and probably also neuropathy in malignant diseases, especially of the bronchus

Summary

A case is described with a lung lesion and peripheral neuritis Evidence is produced that the patient had syphilis, and the progress of the case under treatment suggested that the lung lesion was of syphilitic origin The peripheral neuritis was not thought to be specific

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LYMPHOGRANULOMA VENEREUM (LYMPHOGRANULOMA INGUINALE) *

BY

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So far as can be discovered, British medical literature has produced only one article in which the primary sore of lymphogranuloma venereum has been illustrated (Hanschell, 1938) Two cases, one male and one female, with primary lesions have been described, but not illustrated (Fowler and Walker, 1947) It was felt that it would be of interest, therefore, to describe a male patient, seen in Liverpool in 1954, with a photograph of the lesion which was probably the herpetiform primary

Of 130 cases of lymphogranuloma venereum seen over 19 years by Hanschell (1938), only four showed primary sores, and, although this disease is diagnosed in some twenty cases yearly in the Seamen's Clinic where the present case was seen, the primary lesion does not appear to have been noted previously

Stokes, Beerman, and Ingraham (1944) describe the sore as a herpetiform vesicle with a whitish-grey base, and the incubation period is given as from a few days to 5 weeks It is mentioned that the lesion may frequently be missed by both patient and doctor because of its insignificance and the tendency to heal rapidly and spontaneously It was noted by Hanschell (1938), however, that a primary lesion, which appeared 5 days after the presumed infecting coitus, was still present 3 weeks later

Case Report

A West Indian seaman, aged 23 years, was first seen on November 16 1954, complaining of painful swellings in both groins, which had been present for 2 weeks He gave a history of two previous attacks of gonorrhoea and had last indulged in sexual intercourse in Durban 6 weeks before attending the clinic Three weeks later, while at sea a small penile sore was noticed, but the patient failed to mention it, and only admitted having observed it after the sore had been seen on examination Painful swellings in both groins were noticed 4 weeks after the last sexual intercourse, but apparently had not been associated in the patient's mind with the small penile ulcer No treatment had been sought before November 16

A small circular ulcer with a whitish base was seen on the edge of the prepuce (Figure) The glands in both groins were tender and swollen, adherent to one another and to the deeper tissues, but not to the overlying skin The lymphadenopathy was more marked on the right side No other clinical signs of disease were discovered The blood Wassermann test was negative, as was the lymphogranuloma inguinale complement-fixation test The Frei skin test was positive on November 18

Treatment was begun on November 16 with sulphathiazole 1 g every 6 hours, and on November 18 the ulcer on the prepuce had healed, but the inguinal adenitis was unchanged The patient was last seen on November 22, 1954, when the adenitis was still considerable and painful, and it was thought that hospitalization might be required The patient missed his next appointment, presumably having sailed with his ship, and there was no opportunity of repeating the lymphogranuloma inguinale complement-fixation test to confirm that the infection was of recent origin

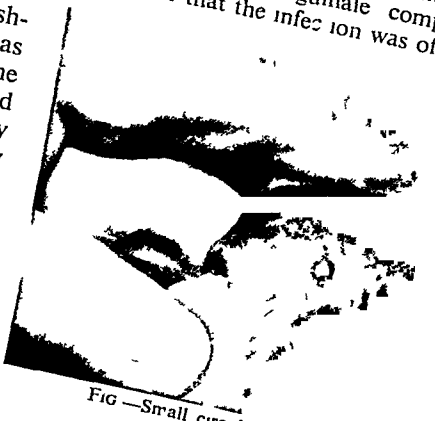

FIG —Small circular ulcer on edge of prepuce

Summary

A case of lymphogranuloma venereum, in which the herpetiform primary was probably observed, is described and illustrated

My thanks are due to Dr E E Prebble, Senior Consultant Venereologist, Liverpool Region, for permission to publish this case, to the Central Photographic Department, Liverpool University, and to the library staff of the Medical Information Division, May and Baker Ltd

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USE OF AN INDIVIDUAL UNSATURATED LECITHIN FROM YEAST IN ANTIGENS FOR THE SERO-DIAGNOSIS OF SYPHILIS*

BY

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Hanahan and Jayko (1952) isolated a pure individual unsaturated lecithin L-α-(dipalmitoleyl)-lecithin, from fresh baker's yeast by adsorption on alumina They showed that hydrogenation of this material produced the corresponding saturated lecithin which was identical with the synthetic L-α-(dipalmitoyl)-lecithin of Baer and Maurukas (1952) The latter compound, when used in combination with cardiolipin and cholesterol, has given antigens suitable for the sero-diagnosis of syphilis (Tonks and Allen, 1953)

Samples of Hanahan's lecithins were obtained and tested in antigens prepared for the Kolmer complement-fixation test and the VDRL microflocculation test Antigens containing the unsaturated lecithin proved to be reactive in both tests Since this pure material is quite stable, as determined by chemical tests, is relatively easy to prepare, and is a solid which can be measured by weighing, it offers promise for use as the lecithin component of cardiolipin antigens

Antigens containing the saturated material showed very little reactivity in the VDRL test when used at a concentration found previously by Tonks and Allen (1953) to be optimal for Baer's synthetic saturated lecithins However, in the Kolmer test, Hanahan's preparation gave results almost identical to those obtained with Baer's material

METHOD OF STUDY

The lecithins were carefully weighed and dissolved in absolute alcohol to give solutions containing 15 mg lecithin per ml alcohol Antigens of various compositions were prepared volumetrically from these solutions and from alcohol solutions of cardiolipin and cholesterol The cardiolipin was obtained commercially (Sylvana) and had been approved for use in antigens The cholesterol solution contained 1 5 per cent pure Pfanstiehl cholesterol (precipitated from alcohol for the Kline test) The lecithin solutions were stored in the dark at room temperature

VDRL Microflocculation Test—Antigens were prepared containing 0 02 per cent or 0 03 per cent cardiolipin, varying amounts of unsaturated lecithin and 0 9 per cent cholesterol One antigen was prepared with the saturated lecithin (0 30 per cent), 0 03 per cent cardiolipin, and 0 9 per cent cholesterol This was the composition found to be most satisfactory when using Baer's synthetic saturated lecithin The various preparations were compared with standard VDRL antigen containing 0 03 per cent cardiolipin, 0 2325 per cent Pangborn lecithin, and 0 9 per cent cholesterol The latter antigen was run as a control in all tests

In order to determine whether different batches of lecithin would give similar results, further samples were obtained from Dr Hanahan In all, three different preparations of each lecithin were tested

The stability of antigen suspensions prepared from one mixture (0 02 per cent cardiolipin, 0 475 per cent unsaturated lecithin, and 0 9 per cent cholesterol) was tested over a 24-hr period Serum specimens were tested at 0, 0 5, 3, 6 and 24 hrs (Table II opposite) Each serum had been divided into several portions and a different portion was tested each time after inactivation at 56° C The antigen suspensions were kept at room temperature in the glass-stoppered bottles in which they were prepared

An antigen mixture (No 8 Table I, opposite) was stored in the dark at room temperature in a screw-capped bottle for 18 months, and its reactivity was compared with that of standard VDRL antigen at regular intervals In addition, an alcohol stock solution of the unsaturated lecithin was tested for stability at room temperature by preparing from it several different batches of the same antigen over a period of 18 months and comparing them serologically Sufficient material however was not available to test the stability of the unsaturated lecithin in its pure solid form

Kolmer Complement-Fixation Test—Antigens were prepared containing 0 0175 per cent cardiolipin varying amounts of unsaturated lecithin and 0 3 per cent cholesterol One antigen was made with the saturated lecithin (0 1225 per cent) 0 0175 per cent cardiolipin and 0 3 per cent cholesterol this composition had been found previously to give the best results with Baer's saturated synthetic lecithin Comparisons were made

* Received for publication February 4 1955

TABLE I

VDRL TEST COMPARISON OF ANTIGENS CONTAINING HANAHAN'S UNSATURATED L α (DIPALMITOLEYL) LECITHIN WITH STANDARD ANTIGEN

Antigen No	Composition (g /100 ml)			Ratio of Cardiolipin to Lecithin	Comparison with Standard Antigen	
	Cardiolipin	Lecithin	Cholesterol		Positive Sera	Negative Sera
3	0 03	0 15	0 9	1 5	Much weaker	Same
1	0 03	0 30	0 9	1 10	Weaker	Same
4	0 03	0 45	0 9	1 15	Weaker	Same
5	0 03	0 525	0 9	1 17 5	Weaker	Same
8	0 02*	0 40	0 9	1 20	Slightly weaker	Same
14	0 02	0 45	0 9	1 22 5	Slightly weaker	Same
15	0 02	0 475	0 9	1 23 25	Very slightly weaker	Same
9	0 02	0 50	0 9	1 25	Very slightly stronger	Some times slightly rough

* The percentage of cardiolipin was lowered to 0 02 per cent so that antigens of higher ratios than 1 17 5 could be prepared

with standard Kolmer cardiolipin antigen containing 0 0175 per cent cardiolipin, 0 2 per cent Pangborn lecithin, and 0 3 per cent cholesterol (Allen and Mason, 1952) Antigen dilutions of 1 300 were found to be optimal for most preparations

To evaluate the various antigens (both Kolmer and VDRL), tests were performed upon individual sera and several dilutions of pooled positive sera which gave negative, weakly positive, or positive reactions with the standard cardiolipin antigens Some idea of the specificity was obtained by testing a small number of sera which had previously been examined with a battery of tests and found to be negative

EXPERIMENTAL RESULTS

(A) With Unsaturated L-α-(Dipalmitoleyl)-Lecithin

(1) *VDRL Test* —The results obtained with antigens containing the unsaturated lecithin, compared with standard VDRL antigen, are summarized in Table I

Fine particles were obtained consistently with all antigens except No 9 when the antigen suspensions were prepared, and when these were mixed with negative sera as prescribed for the test Antigen No 9 showed at times a slight tendency to roughness, but not enough to reject it for this reason All other antigens gave negative pictures very similar to those produced with the standard antigen With positive sera, typical clumping occurred Antigen No 15 (0 02 per cent cardiolipin, 0 475 per cent unsaturated lecithin, and 0 9 per cent cholesterol)

TABLE II

VDRL TEST STABILITY OF ANTIGEN SUSPENSION (IN DUPLICATE) CONTAINING UNSATURATED LECITHIN

Serum No	Readings* at									
	0 hr		1 hr		3 hrs		6 hrs		24 hrs	
1	3	3	3−	3	3	3	3	3	3	3
2	SR	SR	SR	SR	R	R	R	R	SR	SR
3	4	4	4	4	4	4	4	4	4	4
4	3+	4−	3+	3+	4−	4−	4−	4	3	3+
5	—	—	—	—	—	—	—	—	—	—
6	1	1	1	1—	1+	1+	1	1+	1−	1

*R = rough negative SR = slightly rough The plus and minus signs indicate slight differences in particle size It is recognized that the authors of the VDRL test recommend that only the terms positive , ' weakly positive , and negative should be used for reporting results In comparative investigations however it is often advantageous to use numerical readings

was selected as the most consistently satisfactory, although Antigen No 9 also was very similar in behaviour to the standard antigen and sometimes agreed more closely No positive reactions were obtained when 35 sera, which had been previously checked with a battery of serological tests and found to be negative, were tested with Antigen No 15

Table II gives the results obtained in the antigen suspension stability studies which were carried out in duplicate All readings were made by one experienced operator It can be seen that the antigen suspensions retained the same reactivity for at least 24 hrs Heating a suspension at 56° C for 5 min immediately after preparation was found to have little effect This is different from the rather large increases in sensitivity found when suspensions prepared from synthetic saturated lecithin antigens were heated in a like fashion (Tonks and Allen, 1953)

No change in reactivity could be detected in the antigen (No 8) which was stored at room temperature in the dark for 18 months (Table III) Although

TABLE III

ANTIGEN STABILITY STUDY (VDRL TEST—UNSATURATED LECITHIN) RESULTS WITH THE SAME PREPARATION OF ANTIGEN NO 8 COMPARED WITH STANDARD VDRL ANTIGEN AT TWO DIFFERENT TIMES 18 MONTHS APART

Description	May 1953	October 1954
Number of specimens giving stronger reactions with Antigen No 8	12*	12
Number giving same reaction	43	43
Number giving weaker reactions with Antigen No 8	11	7

* With the same serum the difference between readings for the two antigens was never greater than 1+ In May 1953 there were 22 negative seventeen weakly positive and 27 positive (fourteen 4+) sera in October 1954 fourteen negative eleven weakly positive 37 positive (twenty two 4+) This antigen was prepared in the initial stages of the study which may account for the slight discrepancy in relative sensitivity as seen in this Table and in Table I

the complete antigen was thus proved to be stable, the alcohol solution of the unsaturated lecithin gave indications of slight changes when stored under similar conditions Sufficient solid material was not available to prove this conclusively by carefully controlled experiments It is recommended, however, that the alcohol solutions of the pure lecithins be stored in the cold

Three preparations of Antigen No 9, each containing a different lot of the lecithin, showed slight differences in reactivity , however, this may have been due to changes occurring in the alcohol stock solutions, since these were of different ages The results were close enough to indicate that the three batches of lecithin were not grossly different in purity and composition

(2) *Kolmer Test* —The results obtained with antigens containing the unsaturated lecithin, compared with standard Kolmer antigen, are summarized in Table IV Titres of 1 300 were used throughout

TABLE IV

KOLMER TEST ANTIGENS CONTAINING HANAHAN S UNSATURATED LECITHIN COMPARED WITH STANDARD KOLMER ANTIGEN

Antigen No	Composition (g /100 ml)			Ratio of Cardiolipin to Lecithin	Reaction with Positive Sera compared with Standard Antigen
	Cardiolipin	Lecithin	Cholesterol		
12	0 0175	0 245	0 3	1 14	Stronger
13	0 0175	0 250	0 3	1 14 3	Slightly stronger
19	0 0175	0 256	0 3	1 14 6	Same
16	0 0175	0 262	0 3	1 15	Slightly weaker

Antigen No 19 (0 0175 per cent cardiolipin, 0 256 per cent unsaturated lecithin, and 0 3 per cent cholesterol) gave results that were close to those obtained with the standard Kolmer antigen It was found, however, that antigens differing only in containing different batches of the lecithin gave slightly different results This may have been due to changes in the stock alcohol solutions of the lecithin, as found in VDRL test experiments

No positive reactions occurred with any of 48 negative sera which were tested with Antigen No 16

(B) With Saturated L-α-(Dipalmitoyl)-Lecithin

(1) *VDRL Test* —The saturated lecithin proved to be relatively inactive Only with very strongly positive serum did the antigen containing 0 03 per cent cardiolipin, 0 30 per cent saturated lecithin, and 0 9 per cent cholesterol show any signs of clumping With negative serum the particles formed were larger than usual and crystalline in appearance All three batches of the lecithin gave these results

Since Baer's pure synthetic L-α-(dipalmitoyl)-lecithin used in the same concentration gave a satisfactory antigen, it is concluded that the material produced by hydrogenation of the unsaturated lecithin contained an impurity in traces which affected its use in antigens for the VDRL test

(2) *Kolmer Test* —The antigen containing 0 0175 per cent cardiolipin, 0 1225 per cent lecithin, and 0 3 per cent cholesterol gave results which were very similar to those obtained with an antigen of the same composition but containing Baer's synthetic L-α-(dimyristoyl)-lecithin, and with standard Kolmer antigen Baer's synthetic L-α-(dimyristoyl)-lecithin had been found previously to behave similarly to his synthetic L-α-(dipalmitoyl) lecithin It is apparent, therefore, that the unknown factor which decreased the sensitivity in the VDRL test had little, if any, effect in the Kolmer test

Different batches of the saturated lecithin prepared by Hanahan gave antigens of about the same reactivity

DISCUSSION

At present lecithin extracted from beef heart or egg yolk and purified by the methods of Pangborn and others (1951) is being used in cardiolipin antigens The method of purification is somewhat tedious and the end-product is actually a mixture of chiefly unsaturated lecithins The composition varies with the source and it is difficult to produce material of standard sensitivity This lecithin is also unstable in the solid form and is, therefore, preserved in alcohol solution, usually at refrigeration temperatures

The method described by Hanahan gives an individual chemically pure, unsaturated lecithin The method of production is relatively simple and the starting material, fresh baker's yeast, is easily obtained Whether material of the same purity, as tested by the serological methods described above, can be obtained from different batches of yeast, remains to be ascertained It has been shown by Hanahan that his preparations are the same chemically as determined by x-ray diffraction, infra-red spectrophotometry, and other physical and chemical measurements Traces of materials not detectable by these methods might affect antigen antibody reactions, however, and this could be a reason for the slight differences in results obtained with different batches of the lecithins, and also for the inactivity of the saturated lecithin in the VDRL test

Hanahan and Jayko (1952) state that the unsaturated lecithin is quite stable to atmospheric oxidation It is currently believed that oxidation of

such compounds is catalysed by traces of metals such as copper and iron, and it is possible that these are absent in the chromatographed material of Hanahan and Jayko We have found that the unsaturated lecithin is stable for at least 18 months in alcohol solution with cardiolipin and cholesterol, and that antigen suspensions containing it are stable for at least 24 hrs

It is an interesting fact that more of the pure unsaturated lecithin than of Pangborn's lecithin (per unit weight of cardiolipin) is required to produce a VDRL antigen of standard sensitivity

To our knowledge, this is the first time that an individual, completely unsaturated lecithin has been used in antigens for the sero-diagnosis of syphilis On the basis of our work, we conclude that the unsaturated lecithin, if sufficiently reproducible from batch to batch, could be used as the lecithin component in cardiolipin antigens

SUMMARY

(1) A pure unsaturated individual lecithin, L-α-(dipalmitoleyl)-lecithin, was tested as a component in cardiolipin antigens for the VDRL microflocculation test and the Kolmer complement-fixation test for syphilis and gave promising results

(2) A pure saturated lecithin, L-α-(dipalmitoyl)-lecithin, prepared from the unsaturated form above by hydrogenation, was also tested Antigens containing it were successfully used in the Kolmer test but showed little or no reactivity in the VDRL test

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ASYMPTOMATIC NEUROSYPHILIS IN HONG KONG *

BY

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This report presents the results of 1,821 examinations of the cerebrospinal fluid of patients, diagnosed as suffering from latent syphilis, who attended three social hygiene clinics in Hong Kong during the period January 1, 1953, to August 31, 1954

During the last quarter of 1952 and the first half of 1953, a moderately intensive educational campaign against the social diseases was carried out, and a large number of the 1,570 male cases attended the male clinics for a routine blood test in response to lectures, newspaper articles, and film shows

This report only includes patients who stated that they had received no treatment for syphilis, or inadequate treatment, the latter being defined as herbal treatment, less than six intravenous, or penicillin (less than three injections) It must be realized, however, that the clinic patient has a poor comprehension of medical practice and is often unwilling to admit to previous treatment lest this should detract from the consideration given to his present condition

No patient who showed clinical signs of syphilis of the nervous system in any form has been included in this series

The patients comprise 1,570 males and 251 females The male cases are divided into two groups, early latent and late latent syphilis, the dividing line being drawn at a period 4 years after the date of the genital sore

The female group comprises only cases falling within the category of late latent syphilis The small number of cases of early latent syphilis in the female in which examination of the cerebrospinal fluid (CSF) was done during this period is insufficient to be of comparative value

The lumbar punctures were all performed on out-patients in the social hygiene clinics, generally at the second or third visit, but in a small number of cases the test was done towards the end of a 22-day course of penicillin

It is routine practice for the patient to have a simultaneous injection of 2 ml procaine penicillin with 2 per cent aluminium monostearate, and to be given verbal instructions about measures to lessen the severity of any post-puncture headache

Method

The specimen of CSF was collected in two containers, one of which was examined for protein content at the Government Chemist s department and the other for cell content and serological reaction at the Pathological Institute

For the first 8 months of the period, the serological test (STS) performed on the cerebrospinal fluid was the standard Kahn test, and for the latter 12 months the VDRL test was used

As far as can be judged there has been no appreciable difference in the results given by the Kahn and VDRL tests on the cerebrospinal fluid and as the interest of this study lies in the overall picture, no distinction has been made between the result of the two serological tests in this report

It was not possible to arrange for one technician to perform all the serological tests over the 20-month period, but the performance of the test and results were subjected to scrutiny over that period by the Government Pathologist

The fluid was transported to the Pathological Institute from the clinics by special messenger, but due allowance must be made for the fact that 30 minutes to one hour was usually required to transport the specimens The results are shown in Tables I and II (opposite)

Discussion

It was considered important to form an assessment of the extent of asymptomatic neurosyphilis in Hong Kong because general paralysis and syphilitic optic atrophy in the past were thought to have contributed an undue proportion of hospital and clinic admissions

Cook (1948) determined the incidence of both symptomatic and asymptomatic neurosyphilis in Trinidad, and recorded an incidence of 11 5 per cent of asymptomatic neurosyphilis in 417 cases but in determining this figure he excluded cases which showed only an increased cell count in the cerebrospinal fluid

* Received for publication February 17 1955

TABLE I

TOTAL CEREBROSPINAL FLUIDS EXAMINED (MALE AND FEMALE) 1,821

Type of Syphilis	Sex	Number of Fluids	Normal		Number of Cases showing Abnormality									
					Increased Cell Count		Increased Cells and Protein or Increased Protein Alone		Cells and Protein Increased and Positive STS		Protein or Cells Increased and Positive STS		Positive STS only	
			No	Per cent	No	Per cent	No	Per cent	No	Per cent	No	Per cent	No	Per cent
Early Latent	Males	557	500	89 8	13	2 3	14	2 5	2	0 3	4	0 7	24	4 3
Late Latent	Males	1 013	868	85 7	23	2 3	20	2	24	2 3	23	2 3	55	5 4
Late Latent	Females	251	236	94	2	0 8	2	0 8	4	1 6	2	0 8	5	2

TABLE II

RESULTS OF CEREBROSPINAL FLUID EXAMINATION IN 1 570 MALE CASES OF LATENT SYPHILIS

Type of Syphilis	Number of Fluids	Normal		Number of Cases showing Abnormality			
				Cells and/or Protein Increased		Positive STS alone and Positive STS with Increase of either Cells or Protein or both	
		No	Per cent	No	Per cent	No	Per cent
Early plus Late Latent in Males	1 570	1 368	87 13	70	4 45	132	8 4

Granting acceptance of the curative effects of penicillin in the treatment of asymptomatic neurosyphilis, the belief is expressed that, by the detection of an average of six male cases per month of asymptomatic neurosyphilis with marked changes in the cerebrospinal fluid, there should be an appreciable reduction in the incidence of general paralysis and syphilitic optic atrophy in the future

Summary

The selection of the cases, the tests used, and the results of an examination of the cerebrospinal fluid in 1,821 cases of latent syphilis are briefly described The incidence of asymptomatic neurosyphilis was 12 8 per cent in the 1,570 males, 6 0 per cent in the 251 females, and 11 91 per cent for the whole group of 1,821 patients

I am indebted to Dr K C Yeo, Director of Medical and Health Services, Hong Kong, for permission to publish

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ERYTHROMYCIN AND TETRACYCLINE HYDROCHLORIDE IN THE TREATMENT OF NON-GONOCOCCAL URETHRITIS * †

BY

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A total of 158 cases of non-gonococcal urethritis has been treated with erythromycin or tetracycline hydrochloride administered orally Patients who had been previously treated, or had been given less than 6 0 g of the antibiotic, have been excluded, and this paper contrasts the results of 62 previously untreated cases given 6 0 g erythromycin (as 300 mg four times a day for 5 days) with those of 58 previously untreated cases given 6 0 g tetracycline (as 250 mg four times daily for 6 days)

Material

Of the 120 patients examined, 101 were white-skinned, fifteen were Negroes, two were from Ceylon, one from India, and one from Burma , 57 were married, 62 were single, and one was separated from his wife Their average age was 31 years (extremes 20–56) Only 43 had had no previous venereal disease, and the remaining 77 had had between them no fewer than 69 attacks of gonorrhoea, 66 of non-specific urethritis (including one attack of Reiter's syndrome), three of syphilis, three of herpes genitalis, and one each of soft sore, balanitis, and genital molluscum contagiosum

Of the nineteen non-white persons, six had had no previous trouble, but the remaining thirteen had had nineteen attacks of gonorrhoea, ten of non-specific urethritis, one of syphilis, and one of molluscum contagiosum The average number of previous infections was thus 1 6 for the non-white and 1 1 for the white-skinned persons

The infection was acquired from a stranger in 55 cases, from a friend in 39, from the wife in 23, and there was no record in three cases Of the 57 married patients, the infection was apparently acquired from a stranger in 21 cases, from a friend in fourteen, and from the wife in 22

The apparent incubation period was 1 to 7 days in 46 cases, 8 to 14 days in 21, 15 to 21 days in eight, 22 to 28 days in six, and over 1 month in six The incubation period was impossible to assess in 33 cases

The symptoms had been present before treatment for 1 to 3 days in 54 cases, 4 to 7 days in 21, 1 to 2 weeks in 24, and more than 2 weeks in 21 Dysuria was present in 67 cases and absent in 53

Gonococci were excluded in the urethral smears of all cases The Wassermann and VDRL (Harris) tests were both negative in 114 patients, the Wassermann test negative and the Harris doubtful in four, and both tests positive in two The gonococcal complement fixation test was performed on serum from 104 patients it was negative in 97, doubtfully positive in one, positive in five, and anticomplementary in one

Results

The results are shown in Tables I and II In assessing the failure rates, all suspected re-infections occurring within the three post-treatment months have been classified as failures Re-infections occurring after 3 months (the prescribed period of follow-up) have been excluded

TABLE I

RESULTS IN ERYTHROMYCIN TREATED CASES
(6 0 g over 5 days)

Follow up	No Followed	No of Failures	No of Re infections	Cumulative Percentage Failing (including Re infection)
0	62	—	—	—
1–3 days	57	—	—	—
4–7 days	56	3	—	5 4
8–14 days	46	2	—	9 7
15–21 days	40	3	—	17 2
22–28 days	35	2	1	25 8
1–2 months	30	—	1	29 1
2–3 months	21	—	1	33 9
Over 3 months	7	—	—	—
Total	—	10	3	—

Overall failure rates at 2 to 3 months 22 8 per cent of those followed

While failure rates tend to increase as greater numbers are treated and a more prolonged follow-up is obtained, it will be noted that the cumulative failure rate at 2 to 3 months so far compares with a cumulative failure rate of 25 5 per cent with 6 0 g. oxytetracycline or 6 0 g chlortetracycline—both in previously untreated cases (Willcox 1955)

* ... ed for publication June 13 1955

† ... Recent Advances ... April 1955
in the Study

TABLE II

RESULTS IN TETRACYCLINE TREATED CASES
(6 0 g over 6 days)

Follow up	No Followed	No of Failures	No of Re infections	Cumulative Percentage Failing (including Re infection)
0	58	—	—	—
1–3 days	52	—	—	—
4–7 days	51	1	—	2 0
8–14 days	42	—	—	2 0
15–21 days	35	1	1	7 7
22–28 days	30	2	—	14 4
1–2 months	26	4	—	29 8
2–3 months	10	—	—	—
Over 3 months	3	—	(2)	—
Total	—	8	1	—

Overall failure rate at 2 to 3 months 17 3 per cent of those followed

Failures —The average age of the failures was 31 1 years—approximately that of the average of the whole Failure was not related to race, marital status, previous venereal disease, or to the results of the serum tests for syphilis and gonorrhoea Likewise, when the failures were related to mode of infection, the presence or absence of dysuria, or to the apparent incubation period, nothing significant was noted However, when the failures were related to the duration of symptoms before treatment, it was found that proportionately fewer failures were noted in patients in whom the discharge had been present for more than 1 week before treatment than in those in whom it had been present for 1 week or less (Table III)

TABLE III

FAILURES RELATED TO DURATION OF SYMPTOMS BEFORE TREATMENT

Duration of Symptoms (weeks)	No Treated	No Followed	No of Failures	Percentage Failing of those Followed
1 or less	75	67	18	26 9
More than 1	45	42	3	7 1
Total	120	109	21	19 3

This difference may be due to the fact that persons who tolerate a discharge for some time before treatment are less critical and less likely to complain about a minor relapse later

Side-effects —Mild side-effects of diarrhoea, occasional rectal soreness, nausea, etc, followed the general pattern experienced with chlortetracycline or oxytetracycline Of the 120 patients, only one (treated with erythromycin) failed to take the prescribed course

Summary

(1) The results are presented of treating 62 previously untreated cases of non-gonococcal urethritis with 6 0 g erythromycin and of treating 58 previously untreated cases with the same dose of tetracycline

(2) Of the 57 erythromycin-treated cases followed, there were 13 failures (22 8 per cent) Of the 52 tetracycline-treated cases followed, there were nine failures (17 3 per cent) When the results were accumulated to take into account differences in follow-up, the cumulative failure rate was 33 9 per cent for those treated with erythromycin and 29 8 per cent for those treated with tetracycline

(3) Patients in whom the symptoms had been present for more than 1 week apparently responded better than those in whom the symptoms had been present for 1 week or less

(4) Side-effects were relatively few and mild

Grateful acknowledgments are expressed to Eli Lilly and Co Ltd of Basingstoke, England, and Charles Pfizer Ltd of Folkestone, England, for so kindly providing the erythromycin (" Ilotycin) and tetracycline (" Tetracyn ') used in this study

REFERENCE

Willcox R R (1955) *British Journal of Venereal Diseases* 31 89

Brit J venel Dis (1955), 31, 188

INTRAMUSCULAR TETRACYCLINE (ACHROMYCIN) IN THE TREATMENT OF ACUTE GONORRHOEA IN THE MALE*

BY

MILTON MARMELL AND AARON PRIGOT

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Penicillin is used extensively in the routine parenteral treatment of gonorrhoea At times, however, patients report a history of allergy to this antibiotic Oral treatment with sulpha drugs and other antibiotics may be used in such cases, but the multiple dose schedule that is usually followed leaves the patient unsupervized when he takes the medication Often the prescribed directions are not followed, at times the medication is lost, and on occasion it is used for purposes other than intended (such as sharing the medication between sex partners, leaving both undertreated) There is thus a need for a parenteral medication other than penicillin in the armamentarium against gonorrhoea

Recently tetracycline for intramuscular injection† became available Since excellent results have been obtained in the treatment of gonorrhoea with the oral form (Metzger, Marmell, and Prigot, 1954, Marmell and Prigot, 1954), it was deemed advisable to test the efficacy of the intramuscular preparation in this disease This paper presents our data on the use of this antibiotic in 88 cases of acute gonorrhoea

Method

Tetracycline for intramuscular injection is available in vials containing 100 mg of the antibiotic with 40 mg procaine hydrochloride, 46 84 mg magnesium chloride, and 250 mg ascorbic acid The contents of the vial are readily soluble in distilled water or saline solution Two ml of the diluent are added to the vial, thus making a solution containing 50 mg of the antibiotic per ml We used distilled water in our investigations

Details of the methods used have been described by Marmell and Prigot (1955) All the patients in this study showed clinical and laboratory (smear and culture) evidence of gonorrhoea They were considered as cured only if the purulent discharge disappeared and post-treatment smears and cultures were negative, and if there was no relapse during the entire observation period, which was not shorter than 7 days

Treatment consisted of intramuscular injections of tetracycline in the following dose schedules

(*a*) A single injection of 100 mg of intramuscular tetracycline into the upper outer quadrant of the buttock Total dose, 100 mg

(*b*) Two injections of 100 mg each given simultaneously into each buttock Total dose, 200 mg

(*c*) Two simultaneous injections of 100 mg into each buttock on 2 successive days Total dose, 400 mg

Of the 88 cases thus treated only 45 were adequately followed-up after treatment, and these form the basis of this report

Results

The results obtained with the various dose schedules are summarized in the Table

TABLE

INTRAMUSCULAR TETRACYCLINE IN THE TREATMENT OF ACUTE GONORRHOEA IN THE MALE

Dosage	Total Dose (mg)	Number of Cases Treated	Number of Cases Followed up	Cured	Failures	Side Reactions
Single injection	100	8	6	0	6	1
2 simultaneous injections of 100 mg	200	20	6	0	6	0
2 simultaneous injections of 100 mg each repeated after 24 hrs	400	60	33	28	5	0

Only the 45 adequately observed cases who received injections of intramuscular tetracycline were considered Neither the six patients observed out of eight who received a 100 mg injection nor the six observed out of twenty who received a total dose of 200 mg responded to treatment When the dose was increased to 400 mg, 28 (85 per cent) out of 33 patients were cured

The patients who responded favourably were cured rapidly, the thick urethral discharge disappearing within 24 hours

Among the 88 patients receiving tetracycline there was one allergic reaction to the drug manifested by moderate urticaria and slight oedema of the lips This patient gave a history of severe allergic reaction to penicillin which had necessitated hospitalization With this one exception no toxicity

* Received for publication May 17 1955

† The trade name of the Lederle Laboratories for the antibiotic tetracycline is Achromycin and the preparation employed was furnished through the courtesy of that company

of any nature was observed About 40 per cent of the patients complained of local pain at the site of injection This pain lasted in some cases for 48 hours On the other hand, there were patients who minimized the complaint of pain and found it no more severe than with other types of intramuscular medication with which they were familiar Objectively there were no local signs of irritation, such as erythema, induration, or evidence of lesions at the sites of injection

Discussion

Although this study involves a small number of cases it would appear that in adequate doses intramuscular tetracycline is effective in the treatment of acute gonorrhoea The results indicate that 400 mg is the minimal dose that should be used, and that larger doses may be more effective

Intramuscular tetracycline thus lends itself to the treatment of gonorrhoea when parenteral medication is indicated

Summary

Intramuscular tetracycline was used in the treatment of acute gonorrhoea in the male Doses of 100 mg and 200 mg were found to be inadequate, but 400 mg of the antibiotic cured 28 out of 33 patients (85 per cent)

There was one mild allergic reaction in a patient who gave a history of severe allergy to penicillin Approximately 40 per cent of the patients complained of pain at the sites of injection

This investigation was supported, in part, by a grant from the Lederle Laboratories Division of the American Cyanamid Company Pearl River, New York

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Brit J vener Dis (1955), 31, 190

VENEREAL DISEASE PHOBIA IN THE 17th CENTURY*

BY

A FESSLER

Manchester

The sufferer from venereal disease phobia, unfortunately seen so frequently nowadays (Rogerson, 1951), had, according to Richard Wiseman (1676), his predecessor in the second half of the 17th century Apparently at that time the fear of syphilitic infection was widespread, but unlike today, there was then some justification for such a fear Wiseman himself, for example, complained in his treatise on gonorrhoea that the treatment of venereal diseases 'is the most imployment of our profession, the diseases of these parts being most frequently gotten by the most predominant vice of the age"

Wiseman, after describing the "Degrees and Symptoms" of the lues venerea, says

"These dreadful Symptoms have frequently possest the imaginations of some people, who having taken the way to get the Pox are soon perswaded that they have it These men will strangely imagine all the pains and other Symptoms they have read of, or have heard other men talk of Many of these hypochondriack have come to Sir Frac Pr †, in which case he hath been pleased to send for me to consider of their complaints with him They commonly went away from us unsatisfied, nor could they quiet their minds till they found some undertake that would comply with them, which done they were never the better, the imagination in which the Disease was seated remaining still uncured, whereupon presuming they were not in hands skilful enough, they have gone to others and so forwards, till they had ruined both their Bodies and Purses

"There have been three of these people with me lately, one a Tradesman, who told me that since his Wifes death he hath fallen into ill company, and being heated with drink, strayed and got a Clap, for which he had been under several hands, that it had cost him 40 pounds amongst them, but he was still worse and worse I asked him if he had ever a Gonorrhoea? Yea, said he, with great pain in my Back, which still continues, also such a pain in my Nose, that I fear it will fall Upon more particular enquiry I found no such thing only upon straining to make Urine or upon the Close stool he had an involuntary effusion of Seed, which was an old infirmity he had quite forgot I endeavoured to satisfy him that he escaped better than he deserved Whether he continues in the same opinion he seemed to have received from me of his condition I sometimes Doubted, but lately have seen him and been assured, that since he spake with me he had taken no Physick, nor felt any cause for it, he continuing very well'

The question whether the man had ever had gonorrhoea needs some explanation Wiseman, like all his contemporaries,* believed that syphilis and gonorrhoea were one and the same disease and that they differed only "in Degree" Of the diagnosis "gonorrhoea" itself, he shared the belief that "in general it may signifie any flux of Seed from the Body", but he added that "The Moderns have given a larger account of Gonorrhoea, and do find many difficulties of it" He distinguished between three different causes of gonorrhoea, namely,

(*a*) from fault of the vessels,
(*b*) from a fault in the matter of the Seed,
(*c*) infected with a virulency in the Lues Venerea

It was the last form of gonorrhoea which he diagnosed as 'one of the first Symptoms of Lues Venerea' It is important to note that Wiseman regarded a "virulent gonorrhoea only as 'one of the first symptoms" of syphilis Being an excellent clinician, he was fully aware that the existing theory did not always fit the facts, and that syphilis could occur without a preceding gonorrhoea He stated that "sometimes a Gonorrhoea succeeds *not*—where none of the other symptoms have preceeded, a small chancrous Ulcer ariseth between the Prepuce and the glans, above or below, on one side, or in the entrance of the Urethra

Wiseman's patient was suffering from gonorrhoea", but it was a form which was usually

* Received for publication January 9 1955

† Sir Francis Prujean (1593–1666) Physician in London President of the College of Physicians 1650–1654 Dictionary of National Biography

* The humoral pathologists of the 17th century were fully justified in their unitarian view with regard to the venereal diseases A venereal distemper was caused by the disturbance of the humours proceeding from a venomous cause (Salmon 1699) or a venomous contagion (Wiseman 1676) it was a Dyscrasia of all the humors in the Body consisting in a volatile corrosive Acidity (Salmon 1699) However different the symptoms of this type of disturbance of the humours were they had all to be regard d as symptoms of one disease being caused by the same venom or contagion In a similar way widely different diseases are nowadays grouped together on their aetiological basis e g the allergic the psychosomatic and the stress diseases

described as a " simple gonorrhoea " In contrast to it was the " virulent, malignant, or venereal " form of gonorrhoea, a form in which " the white matter turns yellowish and virulent as is contracted in the French Pox " (Salmon, 1686)

Trying to assess the prevalence of venereal disease in former times is always a difficult and hazardous undertaking because the contemporary documents, medical and otherwise, have as a rule the tendency to exaggerate Wiseman's remarks on syphilophobia are therefore of interest because they leave no doubt that in his time a considerable number of persons were treated for a venereal disease who were in reality suffering from something else The causes which contributed to this fact were the then existing concept of venereal disease, the difficulties of diagnosis (though these were well understood by some at least*), the fear of infection among lay people, and an unscrupulous attitude of some members of the medical profession, empirics and quacks included

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* The difficulties which sometimes arose in the differential diagnosis between the French Pox and the King s Evil had already been pointed out in the 16th century by Boorde (1542) and by Clowes (1591) in the 17th century they were again stressed by Browne (1684) and by Wiseman

Brit J vener Dis (1955), **31**, 192

ABSTRACTS

This section of the JOURNAL *is published in collaboration with the two abstracting Journals,* ABSTRACTS OF WORLD MEDICINE *and* OPHTHALMIC LITERATURE, *published by the British Medical Association The abstracts are divided into the following sections Syphilis (Clinical, Therapy, Serology, Pathology, Experimental), Gonorrhoea, Non-Gonococcal Urethritis and Allied Conditions, Chemotherapy, Public Health and Social Aspects, Miscellaneous After each subsection of abstracts follows a list of articles that have been noted but not abstracted All subsections will not necessarily be represented in each issue*

SYPHILIS (Clinical)

Congenital Syphilis in the Absence of Demonstrable Infection of the Parents (Angeborene Syphilis bei nicht nachweisbarer Syphilis der Eltern) FRUHWALD, R (1954) *Z Haut- u Geschlkr*, **17**, 345

The author reports from the Municipal Skin Clinic, Zwickau, Germany, the case of a woman in whom the Wassermann reaction was negative during pregnancy and who showed no signs of acquired or congenital syphilis, and yet gave birth to an infant who developed a syphilitic rash at the age of one month and died a few days later *Post-mortem* examination of the child showed the presence of syphilitic interstitial hepatitis and myocarditis The mother had had two previous pregnancies during both of which serological tests were negative, but on each occasion the infant died shortly after birth without a certain diagnosis having been reached

The father had submitted to serological and clinical examination for syphilis after the death of his first child, with entirely negative results The tests were repeated on both parents after the death of the third child and gave doubtfully positive results in each case Complete clinical examination, including testing of the cerebrospinal fluid, was negative for syphilis, and the mildly positive serological test results reverted to negative within 3 months [but it is not made clear whether this was in response to the antisyphilitic treatment which was given to both parents some time after the death of the third child] It is concluded that after any neonatal death for which no good reason can be found, the possibility of syphilis in the mother has to be kept in mind [This was clearly done in the case of this patient, but without success It seems that a case could be made out for the use of the treponemal immobilization test in such circumstances At any rate, if the slightest suspicion of maternal syphilis is still entertained a prophylactic course of penicillin appears to be justified] *G W Csonka*

Avoidable Congenital Syphilis (Über vermeidbare connatale Lues) BROCK, J, and GRUNER, E H (1955) *Arztl Wschr* **10**, 185 4 refs

The incidence of prenatal and congenital syphilis is declining in Germany as in many other countries, and the authors are of the opinion that it might be possible by means of a programme of prenatal prophylaxis, to eradicate congenital syphilis completely For this purpose they recommend that in addition to the routine blood testing of pregnant women, examination of the retroplacental blood should be carried out, false positive reactions being excluded with the treponemal immobilization test All pregnant women who have previously been treated for syphilis should receive two courses of penicillin during pregnancy, since their syphilis may become reactivated, while babies born of untreated syphilitic mothers should receive immediate preventive treatment with penicillin, even in the absence of clinical or serological evidence of infection (It is pointed out that in Germany, under a law passed in 1953, a pregnant woman must undergo such treatment as may be considered necessary to safeguard the baby against infection while it is the duty of the parents to ensure that the baby receives any treatment recommended by the physician)

The case histories of four babies admitted during the period 1949–51 to the Rothenburg District Children's Hospital, Hamburg with congenital syphilis are quoted In each case the child was apparently normal at birth but developed signs of syphilis and with positive serum reactions 3 to 10 weeks later

[There are serious objections to the replacement of clinical and serological observation of apparently healthy babies born of syphilitic mothers by 'preventive treatment" Amongst other dangers, the possibility exists that a child treated in this way may be stigmatized for ever as having had congenital syphilis The case histories are not at all convincing as evidence of the need for such a policy, because neither the mothers nor the babies had had adequate serological surveillance For example, only one of the mothers had had her blood tested during pregnancy, and in three cases the baby's blood was not tested until syphilis became clinically apparent] *A Fessler*

Late Congenital Syphilis of the Inner Ear—a Sequel of Chronic Osteomyelitis of the Petrous Bone (Die Lues hereditaria tarda des Innerohres—eine Folge chronischer Osteomyelitis des Felsenbeins) NAGER F R (1955) *Pract oto-rhino-laryng (Basel)* **17**, 1 8 figs 24 refs

In cases of late congenital syphilis chronic middle-ear disease is a common occurrence Deafness resulting from changes in the perceptive apparatus, may occur

secondarily as a consequence of spread from the middle ear (tympanogenic) A sero-fibrinous labyrinthitis or a syphilitic osteomyelitis may be produced

In this paper from the University Ear Clinic, Zurich, the author reviews a number of such cases reported in the literature, especially with regard to the histological findings, and adds two cases of his own in which progressive deafness of inner-ear type was noticed and in which the petrous bones were subsequently examined microscopically *post mortem* In one case, in which death was due to miliary tuberculosis, the middle ear was quite normal and the main changes were those of a labyrinthitis In the second the changes were characteristic of a syphilitic osteitis with chronic inflammatory changes in the middle ear which, however, had not affected the bone directly In this case an otosclerotic focus was noticed on one side It is suggested that the bone changes may, in some of these cases, be the result of a haematogenous spread, and it is considered that the histological pictures in the two cases described represented two different stages in the same disease process *G E Stein*

Late Congenital Neurosyphilis (General Paresis and Tabes) (Neurosífilis congenita tardia Paralisis general juvenil—Tabes juvenil) ARNDT, M, and THOMSON, A F (1954) *Acta neurosiquiat argent*, **1**, 3 7 figs, bibl

An account is given of twenty cases of late congenital parenchymatous neurosyphilis (sixteen of general paresis and four of tabes dorsalis) seen between 1940 and 1954 at the Buenos Aires Institute of Neurological Research In only twelve cases was it possible to diagnose syphilis in the parents, only three of whom themselves showed signs of neurosyphilis

The sixteen congenital cases constituted 1 8 per cent of a total of 877 cases of general paresis seen during this period The psychiatric picture was of dementia which either started at a very early age as a generalized mental deficiency or developed during late childhood (average age 13 9) in an apparently normal child In the latter group a catatonic or depressive picture was observed at the onset Pupillary abnormalities were present in all cases inequality and abnormal responses to light being the most frequent Speech disturbances were present in all but one patient, speech being slow monotonous, and slurred in the initial stages, then gradually becoming explosive repetitive and more and more inarticulate and unintelligible until mutism finally developed An intense or partial optic atrophy was found in nine cases Tremor of the hands and tongue was present and was similar to that of the acquired form Hyperactivity and motor restlessness were common The tendon reflexes were reduced in five cases and increased in nine, an extensor plantar response being present in one case only Fits occurred in six cases one patient having up to twenty daily The cerebrospinal fluid showed changes which did not differ from those found in adult paretics On the whole these juvenile cases responded very poorly to malaria and penicillin

The four cases of tabes are also described in detail The onset was at puberty, except in one case in which it was delayed until the age of 34 The clinical picture differed in no way from that of the acquired form *Richard de Alarcon*

Cardiovascular System Syphilis JOHNSON, S A M, JANSEN, G T, and SHAPIRO, H H (1954) *Arch Derm Syph (Chicago)*, **70**, 799 16 refs

A short report is presented from the University of Wisconsin Medical School on the survival and the clinical and serological changes observed among nineteen patients who were treated for cardiovascular syphilis with 4,008,000 units aqueous benzylpenicillin 5 or more years ago The prognostic value of various clinical tests is also discussed

Of the ten patients who had died, five had been suffering from aortic aneurysm, the average survival period being 53 months after the onset of symptoms and 23 5 months after completion of treatment, the corresponding average survival periods for four patients with aortic insufficiency were 74 months and 22 months respectively, while the tenth patient, who was suffering from both aortic aneurysm and aortic insufficiency, survived for 74 months after the onset of symptoms and 44 months after treatment Of the nine surviving patients, two needed another course of penicillin, one on account of accompanying neurosyphilis and the other because the condition of his heart had deteriorated Of the eleven patients whose cerebrospinal fluid had shown pathological changes, six were still alive and in only three of them had the fluid shown signs of improvement

It is concluded from this series that radiological and electrocardiographic indications of left ventricular hypertrophy are prognostically not unfavourable in cases of cardiovascular syphilis, nor does the presence of severe hypertension appear to shorten the survival period Of all the available tests of cardiac function, only the orthodiagram and the functional capacity test are considered to be of prognostic value in this condition The authors also conclude that the results of treatment of cardiovascular syphilis with penicillin are no better than those obtained with arsenic and heavy metals, and that doses up to 10 mega units should probably be given

[It is to be doubted whether such far-reaching conclusions can be drawn from observations on so small a series] *A Fessler*

Relationship between Clinical and Electroencephalographic Findings in General Paresis (Correlaciones clinico-electroencefalograficas en la parálisis general progresiva) MOSOVICH A and WEICKHARDT G (1954) *Acta neuropsiquiat argent* **1**, 43 5 figs 15 refs

A comparative study of the electroencephalographic and clinical features of twenty cases of dementia paralytica was made at St Elizabeth's Hospital Washington, D C The patients ranged in age from 28 to 58 None suffered from epileptic fits and the diagnosis was fully confirmed by neurological and laboratory findings The time of the primary infection was unknown in most cases Six patients showed progressive dementia ele en

a megalomanic picture, two depressive features, and two anxiety and homicidal tendencies

The electroencephalograms (EEGs) before treatment were classified as follows four normal, four 'slightly abnormal", seven "moderately abnormal", and five "frankly abnormal" Of the patients in the last two groups, five showed predominant slow frontal activity and two mixed frontal delta and fast rhythms In twelve cases there was an abnormal response to hyperventilation, with generalized paroxysmal phenomena and greater slowing in the frontal leads The most common abnormalities were frontal slow activity and cortical instability revealed by a dysrhythmic response to hyperventilation No correlation was found between the EEG and the neurological and psychiatric picture A slight improvement in the EEG was observed in some cases after treatment, but it was not significant or conclusive There was, however, a correlation between the initial EEG and the response to treatment, patients with a normal or near normal initial record responding much better to penicillin and malaria *Richard de Alarcon*

Diagnostic Evaluation of Serological Estimation in Eye Diseases 1 Aetiological Significance of Syphilis, Gonorrhoea, and Tuberculosis (Diagnostische Bewertung serologischer Untersuchungsergebnisse bei Augenkrankheiten 1 Aiologische Bedeutung der Lues, Gonorrhoe, Tuberkulose) SIEGERT, P (1955) *Klin Mbl Augenheilk*, **126,** 257 7 tables, 1 fig

This is the first part of a study of considerable interest which leads the author to conclude that exudative granulomatous ocular inflammations constitute a non-specific tissue reaction which is not necessarily related to specific bacterial infections

Positive titres alone indicate the presence of a generalized infection, but do not prove that ocular manifestations are the specific manifestations of such an infection Negative findings on the other hand do not exclude it In tuberculosis a high titre is slightly more reliable with regard to the aetiological inference of ocular manifestations *L Cudkowicz*

The Differential Diagnosis of Tertiary Syphilis in the Eye (Zur Differentialdiagnose der Lues III am Auge) KLEMENS, F, and LUDERS, C J (1955) *Klin Mbl Augenheilk*, **126,** 279 9 figs, 18 refs

Two cases of tertiary syphilis affecting the lids and orbits are reported which were of considerable diagnostic difficulty In the presence of a negative serology biopsy is of some use in differentiating, on histological grounds, granulomatous lesions from those resembling tuberculomata *L Cudkowicz*

False Form of Syphilitic Interstitial Keratitis (Forme trompeuse de keratite interstitielle syphilitique) FRANÇOIS, P, and LESAGE, C-H (1954) *Bull Soc Ophtal Fr*, p 633

Oedematous infiltration of the cornea without precipitates was followed by a crisis of acute glaucoma Iridencleisis was performed and some days later the interstitial keratitis appeared *J Rougier*

Nelson Reaction in the Diagnosis of Chorio Retinitis (L'interêt de la reaction de Nelson dans le diagnostic des chorio retinites) VOISIN, J, and VILLETTE, P (1954) *Bull Soc Ophtal Fr*, p 491

Seven cases of chorio-retinitis are reported The Nelson test is useful in establishing the aetiology, as syphilis can be eliminated when the Nelson test is negative *J Rougier*

Nelson s Test in Ophthalmology (L'inetret du test de Nelson en ophtalmologie) FRANÇOIS, P, and BEAL, F (1954) *Bull Soc Ophtal Fr*, p 639

In a case of irido keratitis, and in one of retrobulbar neuritis, the positivity of Nelson s test has enabled the aetiology to be established, and effective treatment to be initiated *J Rougier*

Congenital Syphilis A Follow up Study with Reference to Mental Abnormalities [In English] HALLGREN, B, and HOLLSTROM, E (1954) *Acta psychiat neurol scand*, Suppl 93, 1 Bibl

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SYPHILIS (Therapy)

Fundamentals of Penicillin Therapy in Syphilis (Las bases de la penicilinoterapia en la sifilis) GUTHE, T (1954) *Act dermo sifiliogr (Madr)*, **46,** 159 3 figs, bibl

The author, who is head of the Section for Venereal Diseases and Treponematoses of the World Health Organization (WHO), outlines the fundamentals of the treatment of syphilis by modern methods A 6-year follow-up study of the results obtained in the treatment of secondary syphilis with penicillin alone and with penicillin in combination with arsenic and bismuth has shown that no additional benefit results from the addition of metal therapy Moreover penicillin is also safer, easier to administer and much cheaper In the author s experience the Herxheimer reaction is not to be feared except sometimes in the treatment of the newborn The new long acting penicillins now available make possible the adequate treatment of syphilis in one or at the most a few injections, whereas because of the prolonged course necessary with arsenic and bismuth only some 10 per cent of patients completed treatment A world survey carried out by WHO showed that some 63 per cent of venereologists use penicillin alone in the treatment of syphilis

The author goes on to stress the importance of the time factor in treatment with penicillin pointing out that the blood concentration of the antibiotic should never be allowed to remain for long below treponemicidal levels during treatment The time required by the treponeme for multiplication is about 30 hrs so that the period during which the blood level is below 0 03 unit penicillin

per ml serum should not last longer than 24 hrs In sero-negative cases of primary syphilis as little as 4 days' treatment with penicillin may suffice, and the results of therapy are not improved by prolonging it for more than 14 days, nor by inducing high blood concentrations of the drug A test dose of 300,000 units of PAM, as recommended by WHO, should produce a level of 0 03 unit penicillin per ml serum, for a period of 72 hrs The following dosage schemes are suggested

(1) 300,000 or 600,000 units PAM given daily or on alternate days to the total dosage required ,

(2) injections of 1 2 or 2 4 mega units PAM at longer intervals corresponding to the size of the dose ,

(3) a single injection of between 4 8 and 6 mega units PAM

The use of abortive and prophylactic treatment with penicillin is discussed and is recommended for the consorts of patients with infectious syphilis and for the contacts of cases of endemic syphilis and yaws In conclusion the author points out the danger of producing resistance to penicillin by giving the drug by mouth or parenterally in comparatively small doses for trifling infections Up to the present, however, there has been no evidence that treponemes are becoming resistant to penicillin *Eric Dunlop*

Studies on the Prophylactic Effect of Locally Applied Antibiotics in Experimental Syphilis AAVIK, O R (1954) *J invest Derm* , **23,** 497 3 refs

Working at the University of Chicago, the author carried out a series of experiments on adult male rabbits to determine the potential prophylactic value of certain antibiotic ointments applied locally against syphilis After mild local trauma to the prepuce, pledgets of cotton wool soaked in a suspension of the Nichols strain of *Treponema pallidum* were inserted into the preputial sac for 3 hrs, the prophylactic preparation under trial being applied to the infected area immediately afterwards or after an unspecified interval in groups of three or four rabbits, while three control animals were similarly treated with " vaseline " and three were left untreated, all animals being inspected every 2 or 3 days thereafter This procedure resulted in the development of typical chancres on the prepuce or glans penis in 96 per cent of control animals in 24 to 63 days, and examination of serum from the lesions by dark-ground microscopy confirmed the diagnosis The following antibiotics in ointment form were tested oxytetracycline aureomycin, erythromycin penicillin neomycin, and bacitracin Calomel ointment *U S P* , and an antiseptic liquid soap containing hexachlorophene were similarly tested Only penicillin had a satisfactory prophylactic effect none of the rabbits treated with this antibiotic developing a chancre whereas only occasional protection was afforded by some of the other applications

In discussing these findings the author admits that his study is of limited value only and that the prevention of a clinically visible local lesion with penicillin or any other drug does not preclude the possibility of general infection Moreover the number of animals used was far too small to allow any valid conclusions to be drawn concerning even the local protective effect of penicillin, although the lack of such effect with the other preparations was adequately demonstrated *R S Morton*

Malaria Therapy in Neurosyphilis (La malariоterapia nei neuroluetici) CARRESCIA, P M , and MASDEA, E (1954) *Riv Malar* , **33,** 247 15 refs

At the Institute of Malariology, Rome, a total of 506 patients, 397 male and 109 female, with neurosyphilis received malaria therapy between 1936 and 1954 The incidence of general paralysis was significantly higher in the males and of congenital syphilis in the females In both sexes paralytic forms were commoner than tabetic forms, and the highest incidence for males occurred in the fourth decade and for females in the fifth The time of onset of neurological symptoms varied widely, but in cases of general paralysis they most frequently developed 16 to 20 years after the primary infection , in the case of tabes there was no peak distribution and symptoms appeared from 5 to 50 years after the primary infection Most of the patients were given malarial treatment within one year of the appearance of neurological symptoms, only active tuberculosis and decompensated heart disease being regarded as contraindications Of the 506 patients 456 were infected by the injection of 7 or 8 ml citrated malarial blood intravenously and 50 by the injection of sporozoites The strains employed were *Plasmodium vivax, P falciparum,* and *P malariae*

The incubation period for *P vivax* was usually less than 5 days when whole blood was given and 23 days when sporozoites were injected The fever of initial invasion was more commonly seen in cases with the shorter incubation periods, and it never occurred in patients who gave a history of previous malarial infection In infections with *P malariae* the peak blood invasion occurred up to the tenth day, and initial fever occurred less frequently than in re-infected patients, whose peak appeared between the eleventh and twentieth days The corresponding data are also given for *P falciparum* infections The total mortality was 4 per cent , fifteen patients dying from benign tertian malaria, one from quartan malaria, and four from malignant tertian malaria , the blood in all these cases was free from parasites at the time of death

The therapeutic efficacy of quinine, chloroquine, " atebrin " (mepacrine), and " paludrine " (proguanil) is assessed in a Table [but the effects of malaria therapy on the neurosyphilitic condition are dismissed with the statement that ' many cases derived notable benefit "] *F Hillman*

Fatal Herxheimer Reactions during Penicillin Treatment for Congenital Syphilis (Reactions d'Herxheimer mortelles au cours du traitement penicilline de syphilis congenitale) MONNET, P and PLAUCHU, M (1955) *Lyon med* , **193,** 169 2 figs, 3 refs

Treatment of Early Syphilis with Terramycin (Tratamento da sifilis recente pela Terramicina) SAMPAIO, M SAMPAIO A , and FERREIRA, N (1955) *Trab Soc port Derm Vener* , **13,** 37 6 refs

Therapeutic Principles in the Treatment of Neurosyphilis [In English] HORANYI, B (1954) *Therap hung*, 4, 7

SYPHILIS (Serology)

Quantitative Studies of Ageing Sera in the Wassermann Reaction with Cardiolipin (Quantitative Auswertung alternder Wa R -Sera mittels Cardiolipin) RUGE, H (1955) *Z Hyg InfektKr*, 140, 521 5 refs

At the University Skin Clinic, Erlangen, 940 samples of syphilitic serum were tested by means of the Wassermann reaction using cardiolipin antigen, and then, after being kept for various periods, were re-tested two or more times at intervals of 4 to over 30 days, sixty samples were examined on four or more occasions, the rest less often A significant and progressive fall in the titre was observed with the ageing of the sera Differences of three or more dilutions were more frequent in specimens obtained from patients with active late syphilis The effect of treatment was also to produce a larger fall in the titre with ageing The factors responsible for this phenomenon are not known

[The detailed results are tabulated and do not lend themselves to abstracting] *G W Csonka*

Behaviour of the Antilipid and Specific Antitreponemal Antibodies after Penicillin Treatment (Osservazioni sul comportamento degli anticorpi antilipoidale e treponemo-specifico dopo terapia penicillinica) MONTILLI, G (1954) *Ann ital Derm Sif*, 9, 458 33 refs

It is known that the adsorption of syphilitic serum with lipoid antigen renders the Wassermann reaction negative but does not prevent a positive reaction to treponemal antigen Adsorption with treponemal antigen, however, renders syphilitic serum inactive to both tests These facts led the author, working at the University of Naples, to investigate the behaviour of the antilipoid and the antitreponemal antibodies in twenty cases of syphilis after administration of 6 mega units depot penicillin given in doses of 1 2 mega units at 4-day intervals The technique of antilipoid antibody adsorption, which is described, consists essentially in incubation and agitation of the serum with a kaolin-beef-heart suspension

In three out of six cases of primary syphilis an initially low titre of antitreponemal antibody disappeared in 24 days after treatment, in the other three cases an initially high titre persisted for 2 to 3 months In five of the six cases the antilipoid antibody remained unchanged at the end of treatment and disappeared in over 30 days In nine out of fourteen cases of secondary syphilis the antilipoid antibody disappeared 30 to 35 days after the end of treatment and in the remaining five cases in 60 days, whereas the antitreponemal antibody never disappeared in less than 90 days, and its titre returned nearly to the original level in two cases after an initial fall

The author found that the higher the initial titre, the more slowly did it disappear The occurrence of some degree of oscillation of the two titres during penicillin therapy is explained on the hypothesis that the reticulo-histiocytic system has a limited capacity to produce antibody The return of the antitreponemal antibody after a course of 6 mega units penicillin is in contrast to the usual complete disappearance of this antibody after treatment with arsenobenzol and bismuth, and the author suggests therefore that lipoid and treponemal antigens should both be used in routine tests as a means of assessing the therapeutic efficacy of the newer antibiotics *F Hillman*

Simple Procedure for the Identification of Non syphilitic Reactions in Serologic Tests for Syphilis in Leprosy Patients PORTNOY, J, and EDMUNDSON, W F (1954) *Int J Leprosy*, 22, 181 31 refs

Studies at the Venereal Disease Research Laboratory of the U S Public Health Service have shown that the addition of choline chloride to the antigen used in the VDRL slide test for syphilis tends to raise its reactivity with syphilitic sera while reducing its reactivity with sera giving non specific reactions A differential test is described in which VDRL antigen is prepared and divided into equal portions, these are centrifuged at 2,500 r p m for 15 min, the turbid supernatants discarded, and the walls of the tubes wiped dry To one tube normal saline is added (Antigen I) and to the other 10 per cent choline chloride (Antigen II), each in an amount equal to the volume of antigen originally centrifuged Using these two antigens, slide flocculation tests are carried out as in the original VDRL technique, the results being read microscopically at a magnification of × 100 and the degree of flocculation with each antigen being assessed on a numerical scale reading from 0 (no clumping or very small clumps) to 4 (large clumps) Where necessary, quantitative tests on serial twofold dilutions of serum in saline starting at 1 in 2 are made and the result for each antigen expressed as the sum of the flocculation values obtained at the various dilutions Where flocculation occurs only with Antigen I, or where the difference between the results with the two antigens is 3 or more, the reaction is regarded as non syphilitic, where the difference is 2 or less the reaction is regarded as syphilitic, and where flocculation occurs with neither the serum is regarded as non reactive

There was good agreement between the results of this differential procedure and those of the treponemal immobilization (TPI) test on sera from 84 presumed non-syphilitic patients, 87 with early syphilis, and 54 with late or late latent syphilis Sera from 255 lepers were also studied, fourteen of these were from patients with clinical or historical evidence of syphilis, six of whom gave the syphilitic reaction in the differential test and positive or doubtful reactions in the TPI test, five were non-reactive in the differential test and four gave negative and one doubtful reaction in the TPI test three gave non-syphilitic reactions in the differential test, two being TPI-positive and one TPI-negative Of the 241 sera from lepers with no evidence of syphilis 21 were found to be TPI positive, fifteen of these gave syphilitic and three non syphilitic reactions and three were non reactive with the differential test Of the remaining 220 sera, which were all TPI negative 153 were non reactive and 67 gave the non syphilitic type of reaction

Substitution of sodium chloride for choline chloride in equimolar quantities gave an essentially similar degree of inhibition of the reactivity of sera giving non-specific reactions, but the " coarseness " of the negative reaction made the interpretation of results difficult

A E Wilkinson

Value of the Quantitative Complement-fixation Test for Syphilis in Leprosy ALMEIDA, J O DE, SOUZA LIMA, L, and CARVALHO, R P S (1955) *Amer J trop Med Hyg*, **4**, 41 17 refs

At the University Faculty of Medicine, São Paulo, Brazil, complement-fixation tests for syphilis, employing a quantitative technique with cardiolipin and antigens from an extract of tubercle bacilli, were performed on samples of serum from 467 patients with treated and untreated lepromatous leprosy after the patients had undergone clinical examination in order to exclude tuberculosis With the cardiolipin test there was a reaction in 28 cases (6 per cent) and no reaction in the remainder With the antigens from tubercle bacilli there was a reaction in 413 cases (88 4 per cent) and no reaction in 54 (11 6 per cent) Blood samples from 133 of the 439 leprous patients who gave negative results in the cardiolipin test were also tested by other techniques for the sero diagnosis of syphilis Of these, 65 per cent gave positive reactions with the Kahn standard test, 36 per cent with the VDRL test, and 12 5 per cent with the Kolmer antigen test

The patients who gave positive reactions in the quantitative cardiolipin test were treated with penicillin as well as sulphones for their leprosy The subsequent serological pattern in these cases was that of non-leprous syphilitic patients It is concluded that the quantitative cardiolipin test is a reliable criterion of syphilitic infection even in individuals with concurrent leprosy

R R Willcox

Intradermal Reaction to Treponemal Protein Antigen in Syphilis (La intradermoreazione con antigene treponemico proteico nei luetici) MARAGNANI, U (1955) *Minerva derm (Torino)*, **30**, 16 43 refs

The intradermal reaction to treponemal protein antigen depends both on individual factors in the patient and on certain factors inherent in the antigen used, such as the mode of preparation and the strain of treponema Figures quoted from the highly controversial literature show that positive reactions have been obtained in 0 to 25 per cent of cases of primary and secondary syphilis in 70 to 100 per cent of tertiary syphilis, and in 30 to 100 per cent of congenital cases suggesting that the test is not diagnostic at any stage of the disease

Using Reiter's treponema the antigenic structure of which is discussed the author working at the Civil Hospital Alessandria has given 0 1 ml of a 1-in-100 dilution of protein from this treponema by intracutaneous injection to 110 syphilitic patients and a number of control subjects A strong positive response was obtained in only three cases of late latent syphilis in one of general paresis and one of congenital syphilis, weak reactions were obtained in another eight cases and doubtful reactions in thirteen No reaction was noted in the remaining 84 cases or in the controls All five patients giving a strong positive reaction also reacted to another non-specific skin test, and one of the patients reacted very strongly to all of four non-specific skin tests Attempts to produce passive transfer of allergy by injecting serum from reacting patients together with antigen into weak reactors gave inconclusive results, and injection of blister fluid from these patients mixed with antigen gave negative results Antihistaminic drugs did not influence the results, but hyaluronidase was found to diminish the response by shortening the time of contact between antigen and antibody Titration of the antigen in an attempt to construct an allergometric curve was unsuccessful, since further dilution rendered the results doubtful

The author suggests that variation in results between different series may be due to differences in interpretation or in the antigen preparation employed Reiter's treponema gives a lipoid, a thermolabile protein, and a heat-stable polysaccharide antigen, and the last-named might be more suitable for skin tests On the whole the author considers that his poor results were mainly due to the nature of the antigen used *F Hillman*

The Serum Protein Picture in Syphilis (Il quadro sieroproteico nella sifilide) POZZO, G, and HOFMANN, M F (1954) *G ital Derm Sif*, **95**, 569 6 figs, 37 refs

This discussion of changes in the serum protein picture in syphilis is presented from the Dermatological Clinic, University of Milan The authors consider that there occurs in syphilis a disturbance of the globulino-poietic mesenchyme, and that the results of a whole group of reactions (the *Reaktions-Konstellationen* of Wuhrmann and Wunderly) should be considered in relation to the stage of the disease The following tests were carried out on 32 patients in all stages of syphilitic infection and on ten with non-specific reactions determination of total serum protein content biochemically and by paper electrophoresis, analysis of euglobulins (the Boselli reaction), and the colloidal tests of MacLagan and Kunkel

Briefly, they showed that in three sero-negative cases of primary syphilis the serum protein pattern and the colloid state were normal In three sero-positive cases of primary syphilis and four of secondary syphilis there was a mild decrease in albumin content with an increase in α-and γ-globulins and a disturbance in the flocculation reactions In ten sero positive cases of latent or cured syphilis there was a very slight increase in the α-euglobulin and γ-pseudoglobulin values, while a number of cases of 'cured congenital and acquired syphilis showed normal values Lastly six cases in which a Herxheimer reaction occurred were analysed In one of these patients who was sero-negative and had a chancre a normal serum protein picture was present, the others showed mild irregularities within the margin of error of the method

The problem of the biological false positive Wassermann reaction is considered in detail The authors suggest that it may be due to

(1) an antibody, such as occurs in yaws or bejel,
(2) some alteration in the serum globulins,
(3) a change in the chemical constituents of the blood [but this last group is not further considered]

In support of the first they cite ten cases of leprosy showing a marked increase in the γ-globulin (mainly euglobulin) value and intensely positive flocculation reactions, in other cases, not associated with any special disease, there may be a mild hypo albuminaemia with increase of α_2-euglobulin or pseudoglobulin value, and also an increase in γ-euglobulin content It is suggested that the last-mentioned is of value in differentiating between biological false positive results and those in cases of latent or congenital syphilis *F Hillman*

Cardiolipin Antigen Nephelometric Measurements 1 HARTMANN, J (1955) *Acta path microbiol scand*, **36**, 82 4 figs, 3 refs

Cardiolipin Antigen Nephelometric Measurements 2 [In English] HARTMANN, J, and REYN, A (1955) *Acta path microbiol scand*, **36**, 129 4 figs, 6 refs

Cardiolipin Antigen VI Examination of an Incomplete Cardiolipin Antigen 1 VII Examination of an Incomplete Cardiolipin Antigen 2 [In English] SCHMIDT, H (1955) *Acta path microbiol scand*, **36**, 141 9 figs, 16 refs

Cardiolipin Microflocculation Reaction for Syphilis on Sera from Patients with Pulmonary Tuberculosis (La reazione di microfloccolazione alla cardiolipina per la sifilide sui sieri di malati di tubercolosi polmonare) MONACO, A (1954) *G Med Tisiol*, **3**, 35 11 refs

Recent Advances in the Serology of Syphilis (Neuere ergebnisse auf dem Gebiet der Syphilis-Serologie) WORTMANN, F (1955) *Praxis*, **44**, 260

Serological Testing for Syphilis in Minnesota A Recommendation for a More Productive Use of Routine Testing KIMBALL, A C, BAUER, H, and BARR, R N (1955) *Minn Med*, **38**, 98 5 refs

Serological Detection of the Treponematoses in African Communities (Comment concevoir le sero-depistage des treponematoses au sein des collectivites africaines) LAPEYSSONNIE, L (1955) *Acta trop (Basel)*, **12**, 29 1 fig, 44 refs

Experimental Production of Non-specific Positive Serological Reactions for Syphilis by Colloid Chemical Means (Ein experimenteller Beitrag zur Erzeugung unspezifische positiver Reaktionen in der Luesserologie auf kolloid chemischen Wege) MOBEST, H (1955) *Zbl Bakt, I Abt Orig*, **162**, 313 7 figs, 12 refs

Acetone-soluble and Alcohol-soluble Fractions of 'Phencer' in the Sero-diagnosis of Syphilis (Il fencor acetosol e il fencor-alcoolsol nella sierodiagnosi della sifilide) PERRIA, M (1955) *Igiene mod*, **48**, 66 4 refs

Biological Diagnosis of Syphilis by Examination of the Saliva A Medico-legal Study (Le diagnostic biologique de la syphilis par l examen de la salive Etude medico legale) L'ÉPEE, P, PAUTRIZEL, –, LAZARINI, –, and SANANES, – (1955) *Ann Med leg*, **35**, 18

Studies of the Non-specific Wassermann Antibodies in Ornithosis (Untersuchungen uber den unspezifischen Wassermann Antikorper bei Ornithose) BRAND, G, and LIPPELT, H (1955) *Arch ges Virusforsch*, **6**, 65 1 fig, 7 refs

Microflocculation [VDRL] Test with Cardiolipin Antigen for the Diagnosis of Syphilis (La microreazione di flocculazione con antigene cardiolipinico per la diagnosi della sifilide) MONTILLI, G, and PISANI, M (1955) *Progr med (Napoli)*, **11**, 68 5 refs

Value of the VDRL Slide Flocculation Test in the Diagnosis of Syphilis CHACKO, C W, RAJAM, R V, KRISHNAMURTHI, N, and GOPALAN, K N (1955) *Indian J med Sci*, **9**, 69 1 fig, 16 refs

SYPHILIS (Pathology)

Untreated Syphilis in the Male Negro Pathologic Findings in Syphilitic and Non syphilitic Patients PETERS, J J, PEERS, J H, OLANSKY, S, CUTLER, J C, and GLEESON, G A (1955) *J chron Dis*, **1**, 127 11 refs

This is a further report of the results of the "Tuskegee Study" of untreated syphilis in the male negro which has been in progress since 1932 under the Venereal Disease Program of the U S Public Health Service at Tuskegee, Alabama The *post mortem* findings in a controlled group of untreated syphilitic and non syphilitic subjects are here correlated with the serological and clinical findings Between 1933 and 1952, 165 (40 per cent) of the 408 untreated syphilitics and 51 (27 per cent) of the 192 comparable control subjects studied have died, necropsy being carried out on 92 (56 per cent) of the former and 33 (65 per cent) of the latter The age distribution in these last two groups was similar, approximately half of each being under and half over 65 at death

Lesions characteristic of syphilitic involvement of the cardiovascular system were found in 89 of the 92 syphilitic subjects Gross examination revealed syphilitic aortitis in 36 cases (40 per cent), the most reliable and most highly pathognomonic signs being linear striation of the intima (32 6 per cent) and saccular aneurysm (7 9 per cent) Microscopically, only marked thickening of the aortic wall and necrosis of the media appeared to be pathognomonic of syphilis Syphilitic aortitis was diagnosed microscopically in 41 (46 per cent) of the syphilitic subjects, while in 4 (12 5 per cent) of the control subjects minimal damage, conceivably due to syphilis, was present Cardiac hypertrophy (heart weight over 400 g) was present in 69 5 per cent of the syphilitic group and 69 2 per cent of the control group and with the exception of syphilitic valvulitis (which was present in less than 10 per cent of the former) no abnormality

of sufficient specificity was found to justify a diagnosis of cardiac hypertrophy due to syphilis Of the 89 syphilitics with cardiovascular lesions, the Kahn test was positive at the time of death in sixty Aortitis was diagnosed in 37 (62 per cent) of these cases, but in fourteen of them the diagnosis was based on either gross or microscopic findings alone and might be considered doubtful The minimum incidence of aortitis in this group was therefore 38 per cent Among the syphilitics in whom the Kahn reaction was negative or doubtful at death, aortitis was diagnosed by both gross and microscopical examination in only two cases

From these findings the authors estimate that in the male negro with untreated syphilis of more than 10 years' duration and who is sero-positive at death, the likelihood of syphilitic cardiovascular involvement being demonstrable at necropsy is approximately 50 per cent Among the 62 cases in which the gross and microscopical findings in the aorta were in agreement there were only two cases in which syphilitic involvement was present but had not been diagnosed clinically, whereas in nineteen cases a clinical diagnosis of syphilitic aortitis was not confirmed post mortem No definite light was thrown by this study on the relation between syphilis and arteriosclerosis

The central nervous system was examined *post mortem* in 46 of the syphilitic group and definite evidence of syphilis was found in only two cases, both in association with syphilitic aortitis The authors remark that "the great scarcity of frank syphilitic involvement of the central nervous system and the complete absence of lesser lesions attributable to syphilis are noteworthy'

No significant differences between the syphilitic and control groups were found in respect of lesions in the other systems of the body, which, it would seem, are not commonly affected by syphilis The primary cause of death in 18 of the 92 syphilitics on whom necropsy was performed was syphilitic involvement of the cardiovascular or central nervous systems, otherwise the distribution of causes of death in both groups was similar

[The Tuskegee Study is unique, and further reports may be expected throughout the further period of 20 years which, it is anticipated, will be required for its completion] *Leslie Watt*

Studies on the Destruction of Red Blood Cells in Paroxysmal Cold Haemoglobinuria of the Donath-Landsteiner (Syphilitic) Type. [In English] JORDAN F L J and SCHLESINGER F G (1955) *Acta med scand* **151**, 107 5 figs 9 refs

Decline in Mortality from Syphilis in Minnesota BELL, E T (1955) *Arch Path (Chicago)*, **59**, 259 6 refs

SYPHILIS (Experimental)

Filterability of *Treponema pallidum* (Ein Beitrag zur Filtrierbarkeit der Spirochaeta pallida) SCHMIDT K (1955) *Zbl Bakt, I Abt Orig* **162** 280 13 refs

Immunological and Biological Studies of Rabbits Infected with Syphilis (Das immunbiologische Verhalten luisch infizierter Kaninchen) MOBEST, H, and DONTENWILL, W (1955) *Z Hyg InfektKr*, **141**, 25 10 figs, 26 refs

GONORRHOEA

Serological Study of *Neisseria gonorrhoeae* WILSON, J F (1954) *J Path Bact*, **68**, 495 23 refs

The author, working at the Sunderland Royal Infirmary, has studied the antigenic structure of 28 "smooth" strains of *Neisseria gonorrhoeae* Details of the serological tests used are given and the causes of the variability which was noted in the reactions are discussed Under optimum conditions *N gonorrhoeae* is usually "smooth" when isolated from acute infections Some suspensions of "smooth" cultures, while not autoagglutinable in 0 85 per cent saline and not agglutinated by normal rabbit serum, may become hyperagglutinable and be agglutinated to an abnormally high titre by rabbit antisera containing agglutinins against the organism, however, both the agglutination reactions and also the power of these strains to absorb homologous antibodies are less specific than with normal strains Some strains are inagglutinable by specific antisera on isolation, but become agglutinable after suitable subculture or after adjustment of the reaction of the suspension to *p*H 6 or boiling it for 30 minutes "Smooth" strains become inagglutinable after mouse passage

Having overcome these difficulties the author demonstrated the presence of eight antigens which are not destroyed by heating at 100°C for 30 min and are part of the protein fraction of the organisms Four of these, designated A, B_1, B_2, and C, behave as group antigens, while the other four (D, E, F, and G) appear to be type-specific Any strain may possess all the group antigens and one type-specific antigen All the antigens may be lost on subculture, but providing A or B remain, the other antigens can be regained

R F Jennison

Clinical Observations on the Prophylaxis of Ophthalmia Neonatorum MANN, I (1954) *Brit J Ophthal* **38**, 734 1 fig

The author suggests that the time has come for a revaluation of the well tried prophylactic measure, introduced by Crede, of treating the eyes of newborn infants with silver nitrate solution She therefore undertook a clinical experiment at the King Edward Memorial Maternity Hospital Perth Western Australia, where this has been the routine practice since the hospital was founded In this area gonorrhoea is uncommon but penicillin-resistant strains of staphylococci are prevalent The trial was carried out on 1,148 infants who were divided into two groups of 569 and 579 respectively and observed for the first 12 days of life In Group 1 the eyelids were cleansed at birth with normal saline solution, in Group 2 one drop of 1 per cent solution of silver nitrate was instilled in addition

Any "stickiness" about the eyes was recorded as discharge This was noted in 100 cases in Group 1 (control group) and in 72 in Group 2, a higher proportion of these cases appeared within the first 4 days in Group 2 than in Group 1, but was also combined with a higher proportion of negative cultures The author suggests that possibly at this stage the discharge without infection was attributable to the reaction to silver nitrate Over the whole observation period potential pathogens were isolated from 17 5 per cent of Group 1 and from 12 4 per cent of Group 2, the organisms found being *Staphylococcus albus* (both haemolytic, and non-haemolytic), *Staph aureus* (haemolytic, coagulase positive and negative), *Streptococcus viridans* (1 case), and *Bacterium coli* (1 case) There were four fairly severe cases of conjunctivitis in Group 1, but none in Group 2, although bacteriologically some of the infections in the latter were potentially worse and included eight cases of double infection The fact that no serious infection actually developed in Group 2 may be considered evidence of local resistance in those treated with silver nitrate In neither group was there any case of severe purulent ophthalmia, and all the infants were discharged from hospital with clean eyes

Sensitivity to antibiotics and chemotherapeutic agents was tested in a certain number of cases Streptomycin alone gave a universally positive result, no organism showing resistance to this antibiotic, aureomycin came next, followed by chloramphenicol, penicillin and sulphadiazine were apparently of little value Clinically, the use of antibiotics is usually unnecessary, but streptomycin would be the antibiotic of choice The majority of infections in both groups cleared up with frequent saline swabbing, clearance in Group 2 being achieved more quickly The author concludes that the use of silver nitrate reduces the incidence of infection, as distinct from discharge, in the first 12 days of life, but that its use is unnecessary in an efficient hospital in a country where the incidence of gonorrhoea is low, but "should still be considered as desirable in primitive conditions among infected populations" *V Reade*

Treatment of Chronic Gonorrhoea with Long acting Penicillin CAMBON, K G, and CAMBON, E N (1955) *Canad med Ass J*, **72**, 221

Symptomatology of Gonorrhoea in the Male NØRGAARD, O (1955) *Ugeskr Laeg*, **117**, 385 8 refs

Acute Gonococcal Peritonitis in Young Girls (Peritonite aigue gonococcique des petites filles) PICARD, R (1955) *Scalpel*, **108**, 409

NON-GONOCOCCAL URETHRITIS AND ALLIED CONDITIONS

Non Gonorrhoeal Urethritis IKEJIANI, O (1955) *W Afr med J*, **4**, 25 1 ref

Bacterial Flora of the Urethra in Non Specific Urethritis WILLCOX, R R (1955) *Canad med Ass J*, **72**, 220 4 refs

CHEMOTHERAPY

Intramuscular Chloramphenicol in Out patient Treatment of Venereal Disease WOOD, C E, OLANSKY, S, and EDMUNDSON, W F (1954) *Arch Derm Syph (Chicago)*, **70**, 625 11 refs

In a study of the suitability of chloramphenicol for the out-patient treatment of venereal diseases the authors gave intramuscular injections of 4 g of the antibiotic suspended in saline or water at intervals of 2 or 3 days Throughout the study no case of intolerance to the drug was noted Results were as follows

Of 24 cases of granuloma inguinale given a total dose of 12 to 16 g of chloramphenicol, success was obtained in 23, the average healing time being 13 days Of 36 cases of chancroid, one injection of 4 g chloramphenicol was sufficient to clear the lesion in twenty, the remainder requiring 2 or 3 further doses before this was achieved The average healing time in this series was 12 2 days Of eighteen cases of lymphogranuloma venereum treated, seventeen were cured within 11 days after a total dose of 12 g chloramphenicol had been given Even better results were obtained, however, in fifteen additional cases of this disease given aureomycin A total of 38 cases of non-gonococcal urethritis were also treated with chloramphenicol, but with less good results than in the other groups

[The treatment described appears to be suitable for out-patient use in cases of lymphogranuloma venereum and granuloma inguinale, but to have no advantages over other methods in chancroid and non gonococcal urethritis] *Robert Lees*

Tetracycline in Genitourinary Infections SANFORD, J P, FAVOUR, C B, HARRISON, J H, and MAO, F H (1954) *New Engl J Med*, **251**, 810 1 fig, 4 refs

Early clinical trials have indicated that gastro-intestinal irritation occurs less frequently after administration of tetracycline than after administration of chlortetracycline or oxytetracycline At the Peter Bent Brigham Hospital Boston, the sensitivity *in vitro* of 200 strains of bacteria, recently isolated from patients with genito urinary infection, to tetracycline was compared with that to the more commonly used antibiotics The methods and materials employed are described in detail On some of the patients controlled therapeutic trials were carried out to correlate sensitivity *in vitro* with clinical response *Escherichia coli* and other Gram negative bacteria were found to be sensitive to tetracycline, but *Aerobacter aerogenes* and organisms of the *Proteus* groups were not It is concluded that tetracycline is a useful drug in the treatment of genito urinary infections *K H Taylor*

Prolonged Reaction to Intramuscular Benzathine Penicillin ANDERSON, H C (1954) *Lancet*, **2**, 1157 1 fig, 9 refs

PUBLIC HEALTH AND SOCIAL ASPECTS

Present Problem in the Control of Venereal Diseases (El problema de actualidad en el control de las enfermedades venereas) CLARK, E G (1954) *Bol Ofic sanit pan-amer*, 37, 154

The author points out that the present mood of extreme optimism following the success of venereal disease control programmes recalls the events which followed the first World War, when a similar optimism was accompanied by a relaxation of control measures and a rise in the incidence of venereal disease consequently occurred

In the United States the incidence of primary and secondary syphilis has fallen precipitately, but this fact should be interpreted with caution because a decline in case-finding activity is always followed by a decline in the apparent incidence Further, discovery of a case of early latent syphilis signifies that a case of primary or secondary syphilis has been missed, and three latent cases are now found for every one of primary or secondary syphilis Moreover, the incidence of early syphilis has recently risen in nine States and eleven of the big cities, while the incidence of gonorrhoea in the U S A is now higher than in any year before 1943, although below the peak reached in 1947, and gonorrhoea is the second commonest notifiable infectious disease In the opinion of the leading American medical organizations concerned with the problem, the programme for venereal disease control should be intensified in the coming years, being directed towards identifying and overcoming the foci of most resistance, and giving more attention to latent syphilis and gonorrhoea It is emphasized that the cost of control measures does not fall in proportion to the reduction in the number of cases for, as the incidence decreases, so the cost of localizing each case rises Thus motives of false optimism or misguided economy should not be allowed to sacrifice a programme which has been, so far, brilliantly successful

[This is a strong warning from an authoritative source] *Eric Dunlop*

Treponematoses from the Point of View of Public Health (Las treponematosis desde el punto de vista de la Sanidad publica) GUTHE, T (1954) *Act dermosifiliogr (Madr)*, 46, 77 7 figs, 28 refs

With the advent of antibiotics and recent progress in laboratory techniques the war against treponematoses has become increasingly effective and in this paper the head of the Venereal Disease and Treponematosis section of the World Health Organization (W H O) outlines the present position Campaigns against venereal disease must be based upon active case-finding by systematic serological examination of population groups and the application of epidemiological principles Laboratories undertaking serological examinations should be restricted in number and should be well equipped, performing standardized quantitative tests and exchanging sera for examination under the control of a central laboratory where treponemal immobilization and agglutination tests may be performed

The incidence of syphilis has fallen in many countries since the end of the second world war, but there are still at least 20 millions of the world population suffering from syphilis, and incidence remains high in many regions, the figure ranging from 14 to 32 9 per cent in parts of Africa, 0 6 to 31 per cent in Afghanistan, 0 5 to 11 9 per cent in Ceylon, 5 to 50 per cent in India, 0 2 to 27 per cent in Egypt, 4 2 to 82 per cent in Ethiopia, and 12 to 15 per cent in certain parts of South America Endemic syphilis exists in Bosnia, Serbia, and many other foci, occurring as "bejel" among the Arab peoples, "njovera" in Southern Rhodesia, and as 'dichucha" among the Bantus of Bechuanaland Yaws, a disease of infancy and adolescence, affects at least 50 million persons, while pinta is a problem in Mexico and Colombia, where it affects 2 per cent of the population although, unlike syphilis, yaws, and bejel, it does not produce physical disablement The essential weapon in the antitreponemal campaign is a sufficiency of penicillin, world production of which exceeded 500 tons in 1953 Systematic treatment campaigns are required wherever there is endemic syphilis, and the part played by W H O and other agencies of the United Nations in assisting such campaigns is described

The economic importance of these diseases is emphasized, for instance, in Southern Rhodesia venereal disease causes the loss of 100,000 working days each year, while in the period 1949–50 the cost to the U S A of psychosis and blindness due to syphilis was more than 150 million dollars On the other hand, it is calculated that the national income of Haiti was increased by 5 million dollars a year as a result of a campaign against yaws *Eric Dunlop*

Private Physician in Venereal Disease Control SMITH, C A (1955) *Sth med J (Bgham, Ala)*, 48, 169

MISCELLANEOUS

Njovera WILLCOX, R R (1955) *Centr Afr J Med*, **1**, 30 5 figs, 15 refs

The condition known as "njovera", which occurs in the native population of certain areas of Southern Rhodesia, is considered to be a form of endemic syphilis comparable with bejel and other extravenereal treponematoses Secondary manifestations—condylomata, mucous patches, laryngitis, and bone pains—are generally the first evidence of the disease, generalized eruptions being uncommon The late lesions are generally of gummatous type, affecting commonly the palate and nasal septum (gangosa), skin, and bones, but the possibility of involvement of the cardiovascular and nervous systems is not ruled out It is suggested that the gummatous stage may be the result of superinfection in sensitized individuals *R Crawford*

On the Clinical and Pathological Aspects of Chronic Benign Plasma-cell Balanoposthitis (Zur Klinik und Histologie der Balanoposthitis chronica circumscripta

benigna plasmacellularis-Zoon) NODL, F (1954) *Arch Derm Syph (Berl)*, **198**, 557 4 figs, 14 refs

Chronic benign circumscribed plasma-cell balanoposthitis was first described as a clinical entity by Zoon in 1952 (*Dermatologica (Basel)*, **105**, 1, *Abstracts of World Medicine*, 1953, **13**, 52) References to it in the literature are infrequent and the author believes that it is often confused with the erythroplasia of Queyrat, but many cases are probably never seen medically Biopsy and histological examination formerly provided the only certain method of diagnosis He then describes a case, seen at the University Skin Clinic, Gottingen, of a 62-year-old man who had developed a red patch on the glans and inner side of the prepuce one year previously The lesion was at first diagnosed as erythroplasia and x-ray treatment given, but later biopsy did not confirm the diagnosis The author describes in great detail the clinical appearances of the lesion, and discusses the differential diagnosis from chemical dermatitis balanitis xerotica obliterans, and balanitis due to syphilis, gonorrhoea, diphtheria, or fungi Only the erythroplasia of Queyrat is considered to present differential diagnostic difficulties

The histological picture found at biopsy is described and illustrated in photomicrographs The most important characteristics were the deposit of quantities of haemosiderin which gave a positive Turnbull-blue reaction and a profound infiltration of the tissues with plasma cells, together with changes in the walls of the small blood vessels The lesion improved under treatment with tannin powder and boracic and zinc ointments The author, differing from Zoon, claims that it is possible to differentiate this lesion on clinical grounds alone, he considers the essential pathological process to be a disturbance of the circulation and permeability of the local capillaries *R D Catterall*

***In Vitro* Sensitivity of *Hemophilus ducreyi* to Several Antibiotics** THAYER, J D, FIELD, F W, and PERRY, M I (1955) *Antibiot and Chemother*, **5**, 132 5 refs

Serum Proteins in Lymphogranuloma Venereum GARROW, J S (1954) *W Indian med J*, **3**, 161 1 fig, 4 refs

Lymphopathia Venereum in the South African Bantu Female ULMAN, H (1955) *S Afr med J*, **29**, 273 2 figs, 15 refs

International Action in the Fight against Treponematosis (*Azione internazionale nel campo della lotta contro le treponematosi*) GIROLAMI, M (1954) *Arch ital Sci med trop*, **35**, 549

Incidence of Yaws in the New Hebrides MILLS, A R (1955) *Trans roy Soc trop Med Hyg*, **49**, 58 7 refs

Recurrence of Experimental Yaws (Framboesial) Infection in the Hamster HILL, K R, and GORDON, C C (1954) *W Indian med J*, **3**, 279 8 figs, 2 refs

EDITORIAL

It has been known for some years that a carefully planned re-study was being made in Oslo of Boeck's famous group of untreated syphilitics, the results of which have been recently published in full (Gjestland, 1955) A recent preview by Clark and Danbolt (1955) indicates that Gjestland's monograph comprises 500 pages, 83 Tables, and twelve illustrations with an annex of seventy pages with thirty Tables and two illustrations The re-study is comprehensive, uses a modern epidemiological approach, and is reported to be a model of meticulously planned and carefully conducted retrospective field research Between 1890 and 1910, Boeck, then Professor of Venereology and Dermatology in Oslo, hospitalized about 2,000 patients with primary and secondary syphilis until their lesions healed without specific treatment He adopted this policy because he was unimpressed by the effects of mercurial therapy and he believed that the patient infected with syphilis ultimately fared better if the body's natural response to infection was not disturbed by incompletely effective remedies Between 1925–27, Bruusgaard, Boeck's successor, obtained follow-up information on 473 of Boeck's group of untreated syphilitics By this study, the Boeck-Bruusgaard material became internationally famous and it exerted a profound influence on our views regarding the prognosis of untreated syphilis It is clear that Bruusgaard recognized some of the weaknesses of the sample studied and others were suggested by Harrison (1932, 1940, 1941) In spite of these reservations, the conclusion drawn from the Bruusgaard study, that about two-thirds of patients with untreated syphilis would escape disabling effects, has been widely taught and accepted

Gjestland, after a preliminary study of a 20 per cent sample of the 1,978 original patients in order to test the record system and tracing procedures, attempted to follow up all the Boeck patients who were Norwegian residents of Oslo in 1890–1910 (1 404 patients) The actual collection of data was preceded by extensive study of possible sources of information, orderly methods of tracing, and careful provision for the collection and recording of information, together with an outline for the analysis of the data to be collected To these meticulous epidemiological techniques may be attributed the highly successful achievement of obtaining usable information in about 80 per cent of the main study group of 1,404 persons Among other items, Gjestland's study has provided answers respecting the incidence of clinical relapse, benign late syphilis, cardiovascular and neurosyphilis, and the role of syphilis in the morbidity and mortality of syphilitics He estimates that between sixty and seventy out of every hundred untreated syphilitics in Boeck's material went through life with a minimum of inconvenience This conclusion and many of the other findings differ little if at all from the results obtained in Bruusgaard's study and our views on the prognosis of untreated syphilis do not seem to require any major modification The present findings reported by Gjestland, however are more firmly based on an 80 per cent sample followed up after 40 to 60 years and analysed on a sex-specific basis This new monograph by Gjestland is obviously an important milestone on the high road of learning in respect of the outcome of untreated syphilis, and the full report will be eagerly studied

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Brit J venet Dis (1955), 31, 204

BACKGROUND OF CONGENITAL SYPHILIS*†

BY

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The study of the medico-social aspect of disease, especially true of congenital syphilis, is relatively new in this country, as is shown by the scanty literature on the subject This might be explained by the need in research of this nature for comprehensive clinical material and for experienced medical staff interested in the problem collaborating with trained and observant social workers

In undertaking this research, which was begun in 1949, we were conscious that within the clinic we had valuable material and resources We would stress particularly our advantage in having available full-time medical and social staff who knew patients individually and could allow those who wished to unburden themselves to chat for a few minutes, whilst allowing those who preferred to do so to pass through quickly It seems that this individual contact helps in preventing default and is, at the same time, an invaluable source of information Continuity is essential when default or research work is involved Full social and default records have been kept for many years and these have been consulted for this survey

Moreover, our area, Tyneside and adjacent districts in which approximately one million people live, can be claimed to be a representative one, as it varies from seaports to cities with heavy industries and to urban and rural districts with coal-mining centres

Field of Investigation

Selection—Of 317 families with one or more congenital syphilitic patients attending this clinic 200, which contained 254 members with congenital infections (200 original patients and 54 siblings), were selected for investigation The 117 omitted consisted of 86 who were rejected and 31 who refused to cooperate The rejections were due to insufficient information (61), to infirmities, such as deafness or low mentality (thirteen) or to family problems (twelve)

Mode of Referral—The largest number of patients 98 (49 per cent) were referred from other hospitals, 48 (24 per cent) were referred by their own doctors, 35 (17 5 per cent) were discovered through the follow up of parents attending the clinic, ten (8 per cent of women) came from antenatal clinics, and nine (4 5 per cent) from various other sources

Sex Ratio—The sex incidence of the 200 original patients was 77 males and 123 females, giving a ratio of 2 3 which also applies to all congenitally infected at present attending the clinic and, further, to those with congenital syphilis (153 males and 219 females) registering for the first time during the decade 1943–1952

Age Groups and Sex—The 200 patients were divided into age groups when they first attended the clinic (Table I) Altogether 25 per cent had received some treatment in the first 5 years of life, but a further 25 per cent did not attend until after 21 years of age

The age groups in Tables I and II are not as given in the Ministry of Health s Annual Return the patients

TABLE I

AGE AT WHICH THE ORIGINAL PATIENTS (200) FIRST ATTENDED CLINIC

Age Group (yrs)	Male		Female		Total	
	No	Per Cent	No	Per Cent	No	Per Cent
Under 5	19	24 6	31	25 2	50	25·0
5–15	30	39 0	35	28 4	65	32 5
16–20	14	18 2	21	17 1	35	17 5
21 and over	14	18 2	36	29 3	50	25 0
Total	77	100 0	123	100 0	200	100 0

TABLE II

AGE OF THE ORIGINAL PATIENTS (200) AT TIME OF SURVEY

Age Group (yrs)	Male		Female		Total	
	No	Per Cent	No	Per Cent	No	Per Cent
Under 5	6	7 8	12	9 8	18	9·0
5–15	24	31 2	24	19 5	48	24 0
16–20	12	15 6	17	13 8	29	14 5
21 and over	35	45 4	70	56 9	105	52 5
Total	77	100 0	123	100·0	200	100 0

* Received for publication August 15 1955

† An abstract from the Report on a comprehensive medico social survey of 200 congenital syphilitic patients and their families

are separated into pre-school and school age, adolescence, and adulthood

It will be noticed that at the time of survey more than half the patients were over 21 years of age (Table II) This was of importance socially as it made it possible to follow their history over a longer period

Results of Investigation

Medical—Initially, 39 (19 5 per cent) of the patients were found to have latent syphilis, later eight of them developed symptoms, infantile syphilis was noted in 28 (14 per cent), and tardive syphilis in 172 (86 per cent)

Of the various clinical manifestations, ocular lesions were the commonest and occurred in 105 (61 per cent) of those patients with tardive syphilis Interstitial keratitis was found in 96 (55 8 per cent), the average age at onset being between 17 and 18 years and the relapse rate 14 per cent It is interesting to note that two patients had Charcot joints, a third was found to have Von Gies joints (both knees), and another showed evidence of cardiovascular syphilis Stigmata were found in 69 (40 per cent) patients, of whom fifty had dental abnormalities, Hutchinsonian teeth were the most common, and occurred in 49 patients

Nine patients (4 5 per cent) presented a negative or doubtful serological result on initial attendance Cerebrospinal fluid was "positive" in sixteen patients, of whom five had latent syphilis, a finding which illustrates the need for routine cerebrospinal fluid investigations

Social—The incidence of illegitimacy of all children in the 200 families (46 out of 831) was 5 5 per cent and was comparable with the rate for England and Wales in 1952 (4 8 per cent), for Tyneside it was 4 1 per cent, from which it would seem that our rate was noticeably higher On the other hand, in 1946 the rate for England and Wales was 6 7 per cent, whilst in 1936 it was 4 1 per cent Spence, Walton, Miller, and Court (1954), investigating a thousand families in Newcastle-upon-Tyne, found the incidence of illegitimacy to be 5 87 per cent, a slightly higher figure than ours Within the families, the burden of illegitimacy has fallen upon the children with congenital syphilis, 24 (9 4 per cent) of the 254 were illegitimate whereas only 22 (3 8 per cent) of the 577 non-infected members of those families were illegitimate, so that the rate for the congenital syphilitic children was more than double that of their non-infected brothers and sisters

The following facts were noted, but their significance could not be assessed because no comparable statistics for the community could be found

Poverty—Thirty-four families (17 per cent) were impoverished during the childhood of our patients, that is to say, the parents, through a low income or poor management or both, were unable to feed or clothe their children adequately While 34 were poorly clothed, only 29 were also poorly nourished It would appear that, in time of difficulty clothing is sacrificed before nourishment for the children

General Health—Seventy (39 per cent) children were absent from school for long periods, chiefly because of ill-health, and in 32 (46 per cent) this absence was directly caused by various manifestations of congenital syphilis

Employment—Of the 125 (47 male, 78 female) patients over school age, 43 women were engaged in home duties The majority of the remaining 82 patients, despite handicaps (mainly physical), were able to earn their livelihood Seven were in subsidized employment of various kinds, and eight were medically unfit for work Poor employment history was associated with bad home conditions or with the deprivation of parental care rather than with health factors in 29 (35 per cent)

Marital Status—Of the 72 marriages made by our patients, five had terminated in separation or divorce Fully half of the married patients had no separate homes of their own, but this factor was not closely associated with unhappiness in marriage

The marital status of the parents fluctuated, at the time of the survey there were seventeen broken homes, fifteen due to separation and two to divorce Few of the separations were legal and few women received maintenance from their husbands In four instances the separation was from a stepfather, our patient having been born of an illicit union

Housing—We took as a standard of overcrowding the presence of more than two persons per room, excluding scullery and bathroom By this standard our incidence of 9 per cent (17 families) compared favourably with that in a survey conducted in our area by Spence and others (1954), whose figure was 19 5 per cent, and was only slightly worse than that of Oxford (7 2 per cent) It was impossible to say whether overcrowding had any bearing upon congenital syphilis as we had no information about housing conditions at the time when our patients were born

Conduct—There was no evidence of over-indulgence in drink or of any promiscuous behaviour among our patients It is possible that this abstemiousness is due in part, at least, to the negative attitude to life of many congenitally syphilitic patients

At least fourteen (7 per cent) of the mothers were promiscuous, but there was insufficient information to draw any conclusions about the fathers, of whom twenty were unknown It was found that sixteen (14 per cent) of the mothers and 33 (45 per cent) of the fathers were heavy drinkers

Child Care—One in four of our patients was unhappy in childhood, as might be expected, they came from bad homes or were deprived of parental care Ten per

cent suffered from neglect, by the mother or the father or both, eight mothers (4 8 per cent) and two fathers (1 4 per cent) had actually been prosecuted for neglect

Thirty of the 54 infected siblings were found through the follow-up of family contacts, thus making a total of 65 (25 6 per cent) patients with congenital syphilis who were found in this way Almost half of the siblings had latent syphilis and none had a negative serology

Cooperation of Patients—Of 176 patients who had completed treatment, 84 (47 7 per cent) did so in the prescribed period As might be expected, the longer the course of treatment, the greater the default rate Of the patients who were under 21 years of age and who were either chronic or complete defaulters, 47 (30 per cent) reflected their parents' lack of cooperation On reaching adulthood, the prospect of cooperation improved significantly Fifty of the patients who had defaulted returned after a lapse of years, those with fresh symptoms cooperating better than those who returned for other reasons When the complete record of attendance during both treatment and surveillance was reviewed, the cooperation of one-third of the patients was excellent, and of another third satisfactory

Search for a Pattern

Five attempts were made to search for a possible medico-social pattern The first attempt was based upon the social class of the family The classification used was that which was made for the 1951 Census (General Register Office, 1951), the family being classed according to the occupation of the breadwinner The second attempt was based on a comparison between the original patients who had been deprived of parental care and the remainder as a control From the medical standpoint, the following investigations were carried out

(1) *On Original Patient*
- (*a*) Age at initial attendance,
- (*b*) Incidence of clinical or latent congenital syphilis

(2) *On Families*
- (*a*) Multiplicity of congenital syphilis,
- (*b*) Total infected persons in family

In neither of these attempts was any significant difference noted in any of the medical investigations

The social investigations according to class revealed the handicap of congenital syphilis when the patients were compared with their non-infected siblings For example, a greater proportion of the congenital syphilitics who were employed were engaged in less-skilled work than their fathers and a much higher percentage were in the lower social classes, whereas the non-infected were not only in the higher social classes, but also a larger percentage had risen into more skilled occupations than their fathers

The patients deprived of parental care showed a definitely inferior social pattern This was especially noticeable in illegitimacy, unhappiness in childhood, forced marriage, and occupational habits They appeared to suffer chiefly in their adjustment to life, in that they tended to be unhappy and unable to form good relationships with others

In the subsequent attempts both medical and social backgrounds were investigated, the medical from the points of view of syphilis and general health, and the social according to the history of the patient and the parents The adverse factors were summed up and the patients were placed into the following categories

O = *nil* adverse,
A = severely adverse,
B = moderately adverse

From the above summation, the patients were grouped as follows

(1) No adverse factors at all (O) four (2 per cent) patients,

(2) At least one factor moderately adverse (B), 39 (19 5 per cent) patients,

(3) At least two factors moderately adverse (BB), 48 (24 per cent) patients,

(4) At least one factor severely and one moderately adverse (AB) 77 (38 5 per cent) patients,

(5) At least two factors severely adverse (AA), 32 (16 per cent) patients

Only fourteen patients (four with OOOO, nine with BBBB, and one with AAAA) had identical coding throughout all four sections

Because of markedly adverse social factors in their personal history, 34 patients were placed in Category A, but their medical history did not show correspondingly unfavourable results when they were compared with the remainder of the 200 patients

Twenty-seven patients were selected because of their severe functional handicaps, which were caused either by congenital syphilis or by other diseases, and their social background was compared with that of the remaining 173 patients Among them a correlation was noted between their medical and their social history, as was seen in poor nourishment and interrupted schooling in childhood and in unemployment and marriage problems in adulthood It is probable that these adverse findings would have been revealed in the consideration of any patients with severe functional handicaps, but there were

other social problems which seemed specially related to congenital syphilis, shown by the higher incidence of illegitimacy and the notably smaller proportion who came from good homes

Recommendations for the Prevention of Congenital Syphilis

The burden of congenital syphilis falls upon the patient, upon his family, and also upon society The present survey was undertaken not merely to gain information but also in the hope of finding a means of eliminating this disease, and we venture to put forward the following suggestions which occurred to us in the course of reviewing the results of the investigation

Routine serological testing of both parties before marriage would prevent much unhappiness and reduce the incidence of congenital syphilis Blood tests could be taken by the family doctor where possible, but equally well at any hospital department other than the Venereal Diseases clinic Regional laboratories should undertake the complement-fixation and flocculation tests and, where necessary, confirmation of their reports should be sought from the Venereal Diseases Reference Laboratory which uses the treponemal immobilization test We feel, from experience, that the interpretation of positive or doubtful findings should rest with the syphilologist

The absolute necessity for serological testing of every woman in every pregnancy, and not merely the first, is clearly shown in the following investigation of the pregnancy history of the 200 mothers which revealed these significant and disturbing facts

(1) 130 (65 per cent) women gave birth to their first syphilitic child after the first pregnancy, 39 (19 5 per cent) at the fifth or later pregnancy ,

(2) 46 (23 per cent) mothers had given birth to more than one syphilitic child

Over the past 5 years, the proportion of women undergoing antenatal serological tests in this area has varied between 54 and 46 per cent , with an annual average of 50 3 per cent It is disquieting to note that the tendency during the last 3 years has been for the incidence to decline

In our local laboratories during the period of this survey, 97,568 blood specimens from blood donors and pregnant women were examined Of 460 (0 47 per cent) found to be "positive", 250 (0 25 per cent) were eventually found to have syphilis

To institute a practice of routine blood-testing would require the cooperation of doctors nurses, midwives (particularly), and patients, and they would all need to be impressed by the value of such tests The argument in favour of serological testing is strong, but it depends upon the provision of adequate laboratory facilities and suitable premises, preferably polyclinics or general medical out-patient departments, where these patients can be examined and, if need be, treated

The problem of diagnosis in expectant mothers and their infected children is emphasized by the high proportion in our series who had latent syphilis (65 per cent of the mothers examined, and 19 5 per cent of the original patients) In the majority of expectant mothers who have syphilis, clinical manifestations are absent or, if present, atypical Similarly, the history of apparently healthy children which many of these women give cannot be accepted without question all members of the family must be investigated

Another danger is that the administration of penicillin for other conditions may temporarily conceal the presence of syphilis in a patient Having noted the anxiety and perplexity arising therefrom, we do not support the view that penicillin treatment, relatively non-toxic though it may be, should be given to the majority of expectant mothers presenting a doubtful serology Similarly, we would record our disapproval of the administration of this drug "just to be on the safe side" to the healthy infant of a treated mother or one whose doubtful serology could not be fully investigated before term A careful serological study, especially if it includes the treponemal immobilization test, should solve the problem, providing we remember that the maternal immobilizing antibodies may persist in the infant's blood until the fourth and even the sixth month of life (Miller, Slatkin, Brodey, Wechsler, and Hill, 1954)

Serological and radiological investigations are especially important in infantile congenital syphilis, as obvious signs of the disease may not be evident at this stage It is, however, necessary to stress that one positive Wassermann result is insufficient basis for a diagnosis of congenital syphilis to be made in an apparently healthy child, and that the cord blood test result may also be misleading Similarly, it has to be remembered that occasionally an initially negative or doubtful serology is compatible with the presence of syphilis

In the absence of corroborative clinical evidence or a definite family history, a patient's infection cannot be classed as "congenital" Subsequent findings, *e g* through family follow-up by the social department, may establish that the patient was actually born with the disease

It cannot be too strongly urged that the sooner congenital syphilis is diagnosed the better In only

14 per cent of our patients was the disease detected in infancy In searching for congenital syphilis it is not wise to concentrate solely on any one age group, in this series, 25 per cent were over the age of 21 years when they first attended

Patients come to our clinic from many sources, *e g*, ophthalmologists, orthopaedic surgeons, general practitioners antenatal clinics, etc Diagnostically speaking, it would seem that there is a need for raising the index of suspicion in the medical and dental professions Fifty of our 200 patients had dental abnormalities, 49 of them having Hutchinsonian teeth, but none was referred by dentists Many persons hesitate to seek dental care, but it might be expected that such abnormalities would be revealed in schoolchildren undergoing routine dental examination Bertram (1950) and Beecher, McIntosh, and McCart (1951) found that of dental abnormalities suspected, in the course of school medical inspections, to be due to syphilis, 24 5 per cent and 32 per cent respectively were, in fact, due to this disease

In attempting to eradicate congenital syphilis from the population it is obvious that the first need is the adequate treatment of all patients with early syphilis The efficacy of antisyphilitic treatment is such that congenital syphilis could be eliminated Modern therapy is well-nigh non-toxic, it is reliable, and its relative safety enables it to be strongly advocated In this department, the concomitant administration of penicillin and bismuth is preferred because

(*a*) there is reason to believe that penicillin alone may not always be completely successful, especially in late pregnancy if the infection is virulent,

(*b*) the therapeutic penicillin blood level is not invariably demonstrated

This reservation is made because of our experience in a series of twelve male patients who were submitted to the same dose of a 'delayed-action" penicillin, one of them failed to give an adequate penicillin blood level even when, after suitable intervals, three other proprietary preparations were used

To be effective, treatment can only be reckoned "adequate' if attendance is regular, and this involves cooperation on the part of the patients and their parents We were fortunate in that the majority of our patients cooperated well, but the small number of defaulters presented a difficult problem In early life, the child's cooperation is a reflection of that of the parents There would be considerably less default if the parents could be made to understand the necessity for regular treatment The shortened therapy practised in modern times has made it easier for patients to attend regularly during the whole course The attainment of adulthood and a more responsible attitude to life, coupled with a knowledge of the nature of the disease from which they are suffering has, in our experience, made for markedly better cooperation

The transfer of a patient from one clinic to another does sometimes cause default, even amongst those who have previously attended well It is felt that if an extract of the patient s case record (V 15) were sent direct to the medical officer of the new clinic, and a report on the social conditions to the almoner, the patient would be recognized on his arrival and made to feel at ease, should he fail to report, his absence would be noted and he could be written to or visited

The adult patient who is mentally capable of understanding the truth has a right to know the nature of the disease from which he is suffering, it is belittling his intelligence to expect him to attend for years without knowing why this is necessary There are, however, many points to be considered before a decision on what he should be told, and when, is reached First of all there is the parental background—disharmony might be caused in an otherwise happy home if the information is given too bluntly It is well that it should be known whether the parents are alive or dead If either or both are living and have shown themselves cooperative, their feelings in this matter should be respected, but it may be necessary to override their wishes if they have been obstructive or neglectful Should the parents have died before the need to tell the patient arises, the problem is somewhat simpler—clearly, it is very desirable that his respect for his parents should not be lessened, but at least the danger of his making some unwise remark at home no longer exists

In this department, if a patient has reached the age of 21 years or is about to get married, the medical officer is given full information by the almoner about the home background and then he decides how much of the truth should be told He will tell the patient he has syphilis, but may withhold the fact that it has been inherited and merely say that it might have been caused by accidental infection in childhood That the disease has been contracted innocently must in every case be impressed upon the patient

Of the 98 patients in our series who were told the truth, eighty apparently took it well, seven appeared indifferent and perhaps did not realize the implications, seven took it badly and have been worried ever since, and four were definitely embittered From experience, it was found that patients who had not been told the truth by us were exposed to the grave danger of learning it from undesirable sources

The results of this investigation convinced us of the need for polyclinic treatment of congenital syphilis, and this is now given in the out-patient department of this hospital Here, mothers receive treatment with their children, women with doubtful antenatal serology are investigated, as also are the family contacts of infected patients It is a great help to be able to direct patients to a clinic that is not associated solely with the diagnosis and treatment of venereal disease, since many of them would be ashamed to be seen entering such a place

Our results show the urgent need for testing all members of the family of a patient suffering from congenital syphilis, and those children of a syphilitic mother born subsequent to her infection Almost half (254) of 534 contacts examined were proved to have syphilis, and a quarter of the 254 congenital syphilitics were discovered through these routine examinations In this sphere the family doctor can play a most helpful part, he, more than any other medical practitioner, can take the blood specimens without arousing suspicion

We would place on record our thanks to the Newcastle-upon-Tyne Regional Hospital Board for financial aid which made this research work possible, and to the Printing Section, Department of Photography, King's College, Newcastle-upon-Tyne, for the printing of the complete paper

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VALUE OF THE KAHN TEST IN AFRICANS*

BY

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Stokes, Beerman, and Ingraham (1944a) discussing the occurrence of biologic false positive (BFP) results with serological tests for syphilis, wrote

> Inevitably, faith in the positive is being undermined and, with it, the tremendous positive efficiency and low margin of error of serologic test procedure for syphilis in the aggregate is momentarily submerged

This observation is even truer today

Originally it was believed that the various standard tests were specific for syphilis, and that the finding of a positive test was proof that the patient had syphilis The fact that the tests could be undertaken with a non-specific antigen extracted from beef-heart, raised doubts as to the specificity of the tests It subsequently became apparent that positive results were sometimes obtained from patients other than syphilitics, and with the passing of years, more and more causes of false positives have been reported, together with reports of false positives for which no cause could be ascribed, so that now there is a formidable literature on the subject The *British Journal of Venereal Diseases* (1951), in an editorial devoted to the subject, suggested that the increasing awareness of the problem of the BFP could be ascribed to two causes

(*i*) The mass blood testing of blood donors, antenatal patients, etc which had become common during and since World War II

(*ii*) That the general sensitivity of serum testing might have risen to such a degree as to endanger specificity

When serological tests for syphilis (STS) were carried out only on those who definitely had, or who were suspected of having, syphilis then obviously the opportunities for observing false positives were few With the advent of mass testing, and, in some countries, of compulsory marital and pre-enlistment testing, the opportunities of observing false positives became greatly increased and many serologists, to avoid the false negative result have introduced modifications to increase sensitivity

The consensus of opinion is that such false positives do occur, and are not due to masked syphilis But Heywood (1952), in a paper read before the Medical Society for the Study of Venereal Diseases, stated that

> Experience has proved that, whatever their fundamental nature, present-day serological tests for syphilis are, in practice, both highly sensitive and highly specific, and with appropriate safeguards to exclude temporarily false positive reactions, a positive reaction means that the patient has been infected with syphilis at some time in his life

He further considered that the concept of biologic false positive reactions had no practical importance That Heywood's views were not generally acceptable was obvious during the discussion that followed his paper

Problem of the BFP Reaction

Definition of the BFP Reaction—Price (1949) defines BFP as the repeatedly positive blood test given by the serum of a patient who fails to yield any evidence of the disease [syphilis]

Moore and Mohr (1952a and b) further subdivide BFP reactions into the following categories

> (*a*) *Acute BFP reactions* which occur during or shortly after a variety of non-syphilitic infections and disappear spontaneously within a few days weeks, or months
>
> (*b*) *Chronic BFP reactions* wherein reagin persists in the blood over many months or years, perhaps even for life

Value of Different STS—Opinions are very varied as to the specificity of the different forms of STS Kvittingen, Cutler McCullough Rose Ford Tampi Sen and Lakshwir (1952) reporting from India on parallel testing with the Qualitative Kahn the Meinicke and the VDRL tests recorded remarkable agreement between them Schmidt (1953) reporting from Copenhagen on a series of 5 250 presumably non syphilitic patients found the incidence of BFP reactions with the Wassermann using lipoidal antigen higher than with the standard Kahn test which had the same specificity as the Wassermann with cardiolipin antigen Wilkinson (1954) using the treponemal immobilization (TPI) test as a yardstick, found the specificity of various STS to be in the following order

(*i*) Price Precipitation Reaction
(*ii*) Standard Wassermann
(*iii*) Kahn
(*iv*) Cardiolipin Wassermann

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Moore and Mohr (1952a) summarize the position thus

> Although it is customary for each author-serologist to claim that his test has some special virtues that set it apart from others, it is none the less true that all of these tests depend on a basically identical physico-chemical and immunological phenomenon

Since all STS depend on the same phenomenon, and a non specific one at that, it seems probable that all of them will be more or less liable to BFP reactions

Value of Verification Procedures —Various attempts have been made to recognize a specific antibody of syphilis among the complex of substances collectively known as reagin, the presence of which in the serum is the basis of all the different STS Attempts to show whether reagin produced in treponematoses and in BFP reactions are qualitatively identical have so far failed The two best known verification procedures are the Kahn verification test and the Neurath euglobulin inhibition phenomenon, neither of which has been found to be satisfactory Falcone, Harris, Olansky, Salvado, and Cutler (1953) tested the Neurath inhibition phenomenon on 436 patients in Guatemala and found that the results were dependent to a large extent on the type of antigen used, and that it added no significant information to that given by STS Roy, Hill, Gowdey, Kelcec, and Rein (1953) compared results with the Neurath phenomenon and the TPI test in a series of 96 patients, including known syphilitics, problem cases, and presumed non syphilitics They found that the Neurath test was in agreement with the clinical diagnosis in only 64 5 per cent of the cases, whereas the TPI test was in agreement with the clinical diagnosis in 95 7 per cent of them That is to say, the clinical diagnosis was a better guide to the presence of syphilis than was the Neurath phenomenon Harrell (1953) compared the results of the TPI and Kahn verification tests in 48 problem sera (diagnosed clinically as BFP, having positive STS, and no history, signs, or symptoms of syphilis) He found that the results of the Kahn verification test differed from the TPI in 30 per cent of cases Rein and Kostant (1949) state that the Kahn verification test has been unable to distinguish consistently between positive and false positive serological reactions Moore and Mohr (1952a) state that the Kahn verification test and the Neurath phenomenon have no practical merit Kolmer and Lynch (1953) express a similar opinion

Value of Special Antigen —The isolation of cardiolipin, a serologically active phospholipid, from beef heart by Pangborn (1941) was hailed as a great step forward, as it was hoped that the replacement of the relatively crude heart extracts, from which the lipoidal antigens are manufactured, by pure cardiolipin would eliminate the occurrence of BFP reactions

It is generally accepted that the use of cardiolipin antigens has made the STS more specific Andujar, Anderson, and Mazurek (1948), reporting their experience with 24,609 blood samples, commented on the generally superior specificity with cardiolipin antigens, though they noted BFP reactions with cardiolipin as well as with lipoidal antigens Kolmer and Lynch (1953) state that cardiolipin antigens are less likely to give BFP reactions, and stress that this is particularly so in malaria Klein and Leiby (1948) reported that six (26 per cent) of 23 cases of malaria gave positive Kahn results, while with tests using cardiolipin antigen no positives were found Stout and Cutler (1951), working in Guatemala, found a much higher proportion of positives using lipoidal antigens (Kahn and Mazzini tests) than with cardiolipin antigens (VDRL and Kahn tests) Stout, Guzman, and Scrimshaw (1952 b) subsequently examined children from a number of Central American schools (only one of which was in a malarious district), using a battery of tests Not every child was submitted to all the tests, but between 1,500 and 2,000 sera were submitted to each test They found the following positive results with lipoidal antigens Mazzini 33 2 per cent , and Kahn 17 4 per cent , whereas with tests using cardiolipin they found VDRL test 2 6 per cent positive and Kline 3 1 per cent positive There was no evidence of a high incidence of congenital or of latent acquired syphilis among the children They therefore concluded that there was a much higher incidence of BFP results using lipoidal antigens Levitan, Aragon, Cutler, Funes, Portnoy, and Paredes (1952) reported similar findings with 438 children from a Guatemala orphanage Idsoe, Guthe, Christiansen Krag and Cutler (1954) commented on the tendency for cardiolipin antigens to give fewer BFP reactions Tompkins (1949) carried out STS on non-syphilitic patients 2 weeks after successful vaccination, and concluded that BFP reactions were commoner with lipoidal than with cardiolipin antigens, and with precipitation than with complement-fixation tests Klein, Konwaler, Sears Berke, and Leiby (1950), however, having examined 8,851 presumably non-syphilitic sera by the lipoidal Kahn test and a cardiolipin slide test, found no difference in the specificity of the two tests, both being in the region of 99 per cent Price (1954) concluded that the liability to obtain non-treponemal reactions was greater when using cardiolipin-type antigens than when ordinary standard antigens are used Stout, Harris and Olansky (1954), summarizing the position of STS in the U S A in 1954, state that the only lipoidal test still favoured is the Kahn test They stress that, though cardiolipin antigens will reduce the incidence of BFP reactions, they will not entirely eliminate them

More recently, claims have been made for the use of another phospholipid, sitolipin, extracted from soya bean Pirila (1954), testing a sitolipin antigen in the VDRL test against the standard Kahn using lipoidal antigen in 1,535 patients who had been thoroughly examined clinically, found fewer BFP reactions with the sitolipin test than with the Kahn test Rein, Kelcec, and Rosenfield (1951) compared the results with sitolipin and cardiolipin antigens in three different STS (VDRL, 1,682 sera , Rein-Bossak, 1,798 sera , and Kent complement-fixation, 624 sera) They obtained practically identical results whatever type of antigen was used

Value of Using Several Tests —It has been repeatedly observed that, where BFP reactions occur, they often do not show positive in all of a battery of different

tests Schmidt (1954), reporting on the results of routine STS on blood donors in Copenhagen, concluded that when several or all of a battery of STS were positive this was strong evidence of syphilis as opposed to BFP reactions Kolmer and Lynch (1953) advise the use of two or three tests "since there is as yet no best serological test for syphilis" Stokes and James (1949), discussing their experience with 43 BFP cases, advise the use of a battery of tests, and describe serological discord as a warning of probable BFP reaction, though they point out that serological discord is also found in syphilis after previous treatment Thomas, Landy, and de Mello (1950) also commented on the occurrence of serological discrepancies, noting them particularly when the results with flocculation and complement-fixation tests were compared, but they observed such discrepancies both in BFP reactions and in true syphilitic cases

Treponemal Immobilization Test—Until the description of the treponemal immobilization (TPI) test by Nelson and Mayer (1949), all serological tests for syphilis depended on the demonstration of the presence of non-specific reagin The TPI test depends on the detection of a treponemal antibody distinct from reagin Early reports suggested that it was highly specific, positive results only being obtained from patients with syphilis or allied treponematoses Subsequent reports have not contradicted the original opinions as to the value of the TPI test, not only with regard to specificity but also in reproducibility

Magnuson and Thompson (1949) and Thompson and Magnuson (1951) reported on the specificity of the TPI test and its value in recognizing BFP reactions Nelson and others (1950) reported that fifty patients clinically diagnosed as having latent syphilis all gave positive TPI tests, and twelve patients who were clinically BFP cases all gave negative TPIs Miller and others (1952a, b 1954) reported on their experience with 455 TPI tests and commented on its specificity and value in recognizing BFP results Chacko (1953) showed experimentally that the immobilizing antibody was stable under varying conditions of temperature and serum contamination, a most important point if specimens are to be sent from a distance, particularly in the tropics Chorpenning (1953) reported the specificity of the TPI test as 99 per cent or over Olansky Harris, and Hill (1953) using the TPI test in the elucidation of BFP reactions in patients inoculated with malaria, obtained confusing results which they ascribed to poor reproducibility of the TPI test Roy and others (1953) and Boak Miller and Carpenter (1954) both reported a high degree of reproducibility of the TPI test (97 4 per cent in Boak s series) in contradiction of Olansky s findings Wheeler Van Goor and Curtis (1954) reported a reproducibility of 93 per cent and 96 per cent with the TPI test and also commented on its specificity and value in elucidating BFP results Nielsen (1954) and Zellmann (1954) made similar comments

The drawbacks to the TPI test are technical complexity and expense Its satisfactory performance necessitates a highly skilled team of laboratory workers permanently on guard against errors Ledbetter (1954) discussing the use of the TPI test in the United States Navy, has stressed the necessity of training and maintaining such a team While some technical simplifications have been introduced since Nelson's description of the technique, the TPI test still remains a most complicated laboratory procedure and one which cannot be attempted in any but the best equipped and staffed laboratories It also remains an expensive test, and cost alone will preclude its wide use in most backward countries Nielsen (1954) estimated that only thirty laboratories throughout the world were performing the TPI test as a routine Possibly the immune adherence test recently reported by Olansky, Harris, and Casey (1954) or some other similar test simpler than the TPI may prove the ultimate answer The present position is that, though the TPI test is the answer to the problem of the BFP reaction, it is not a practical proposition in many world areas, particularly in the tropics Moore (1949) says

> Though Nelson s work on treponemicidal antibody is of the highest importance to the eventual development of a wholly new, more sensitive, and perhaps absolutely specific serological test for syphilis it is certain that at least for the next decade reliance must still be placed on the present non specific lipoidal antigens for the detection of the equally non-specific reagin

Probably decade is an underestimate for many world areas

Nature of BFP

Technical False Positive—Kolmer and Lynch (1953) point out that many BFP reactions are due to technical errors in the taking of specimens in the performance of the STS, or in the reagents used Technical false positives are especially liable to occur in backward countries where much of the taking and labelling of blood specimens, book-keeping care of glassware etc has to be undertaken by semi skilled or unskilled personnel Lees (1951), discussing the problems of venereal disease in Africa stressed the need for a simple serological test for syphilis of high reliability which could be done by an African technician He also stressed the need for trustworthy batches of antigen Kvittingen and others (1952) reporting from India mentioned the variability of different batches of antigen as a cause of anomalous results Idsoe and others (1954) state that

> Most variations in sensitivity and false positivity result from individual differences both in the patient and in the test procedures rather than in the underlying differences in the process being tested for the behaviour of the reagin

One other factor of special importance in the tropics is the tendency of sera to deteriorate when they have travelled long distances especially under adverse climatic conditions (Evans 1954) Kahn (1954) considered that he could distinguish a typical serological pattern in sera but subsequently found that this only occurred in sera which had travelled long distances free from Jamaica and was not present in fresh sera from cases [illegible]

Most technical false positives (and negatives) can be readily eliminated in all cases with anomalous [illegible]

by repeating the test or tests on a second fresh specimen of serum with different antigen and possibly at a different laboratory The occurrence of frequent anomalous STS results at a laboratory is an indication for a careful review of technique and technicians, a check on the purity of all reagents used, and for testing the antigen in use against a standard antigen (if possible from the a.. erologist s laboratory)

Strength of BFP Reactions—The belief that BFP reactions were characteristically of low titre was at one time widely held Allison and Dick (1954) reporting a case of a BFP result associated with virus pneumonia state that BFP reactions are usually weak and a strongly positive reaction is often regarded as being caused by syphilis unless proved otherwise Schmidt (1954), reporting on BFP reactions among blood donors, found the greatest number of them among the lower degrees of potency Kahn (1954) states that BFP reactions are usually weak and of low titre Stokes and James (1949), however, reviewing their experience with 43 BFP reactions from private practice, found quite a high proportion had high titres with STS

The advent of the TPI test has cast further doubt on the generalization that BFP reactions are only weakly positive to STS Miller, Slatkin, Brodey, Weschsler, and Hill (1954) concluded that the serological titre was of no certain significance in excluding BFP results, since patients with high serological titre were sometimes found negative to the TPI test and *vice versa* Wilkinson (1954) found that, while a majority of BFP reactions (confirmed by TPI testing) are low-titred, there are sufficient with high titres to make any generalization unwise Wheeler and others (1954) made a similar observation

Duration of BFP Reactions—Kolmer and Lynch (1953) state that most BFP reactions become negative in 3 to 6 months, sometimes in a few days Price (1949) found that on serial testing the reaction remained positive for a relatively short time, and gradually subsided to negativity without treatment Kahn (1954) states that BFP reactions may continue for a few weeks to several months It is probable that, as suggested by Thomas and others (1950), falling titres which become negative in untreated patients who deny the possibility of syphilis are rarely, if ever, due to syphilis However, their further statement, that positive STS results which do not show a declining titre in the absence of syphilitic treatment mean, in the majority of cases, that the individual has or has had syphilis, would not be generally accepted now In short, an STS result that becomes negative in a short time without treatment is almost certainly a BFP reaction, but no conclusion can safely be drawn that, because the tests remain positive for months or years, the patient therefore has syphilis

BFP Reactors—Kahn (1950a, 1953, 1954) has described his universal serological reaction By this test, which is a series of quantitative set-ups with different concentrations of saline solution and read after different periods of incubation in the refrigerator, he describes a serological pattern for health and in certain diseases He states (1950c) that in certain normal healthy individuals the serological pattern comes very close to the serodiagnostic zone, and that such individuals are particularly liable to give false positive reactions Stokes and James (1949) also state that some individuals tend to produce reagin more easily than others, *i e*, are BFP reactors They also suggest that, when a syphilitic has gained sero-negativity he may again become positive under the influence of agents such as inoculation, malaria, etc, which tend to cause BFP reactions

Other Factors in BFP Reactions—A wide variety of conditions has been shown in the past to be associated with the occurrence of BFP reactions It is believed that almost any condition which causes tissue breakdown may result in a BFP reaction in individuals prone to give such reactions (BFP reactors) The most common causes of such BFP reactions are acute infections of which outstanding examples are infectious mononucleosis, pneumonia (especially virus pneumonia) influenza scarlet fever typhus meningitis tuberculosis, relapsing fever, rat-bite fever, Weil s disease, typhoid fever, trypanosomiasis, kala-azar, and especially malaria The BFP reaction in such cases usually requires, according to Kahn (1954) about 2 weeks incubation after tissue breakdown has commenced It is of the acute type described by Moore and Mohr (1952a), and becomes negative in a short time without antisyphilitic treatment Of similar nature is the BFP reaction occasionally found after inoculation, especially vaccination and inoculation against yellow fever or typhoid Talmage, Dunn, and Breazeale (1946) found that of 692 battle casualties, 253 (34 5 per cent) had a positive STS, in only one of which was syphilis thought to be the cause

Both jaundice and cirrhosis of the liver are quoted as occasional causes of BFP reactions However Stout, Aguirre and Scrimshaw (1952) could find no correlation between the occurrence of BFP reactions and of positive cephalin cholesterol flocculation tests for liver function among school children in Central America Similarly, it has been suggested that hyperproteinaemia might be associated with BFP reactions Stokes, Beerman, and Ingraham (1944b) give the incidence of BFP reactions in hyperproteinaemia as 23 per cent Wills and Bell (1951) found a high proteinaemia among the natives of Fiji and also a high rate of positive STS, they mention however that yaws is common Cardon and Atlas (1942) found that electrophoretic studies did not corroborate the belief that BFP reactions are associated with hyperproteinaemia Cooper, Craig, and Beard (1946) could find no basis for the diagnosis of syphilis by electrophoretic analysis of sera, or for a differentiation between individual syphilitic and BFP sera Stout, Mendez, Guzman, and Scrimshaw (1952) could find no relation between the level of serum proteins, albumin-globulin ratio, or level of α-, β-, or γ-globulin and the occurrence of BFP reactions in school children in Central America

Evidence as to the possible effect of dietary deficiencies in causing BFP reactions is conflicting Meinicke (1952) reported converting presumptive BFP reactions to negative in undernourished patients by the oral administration of lecithin Stout, Guzman, and Scrimshaw (1952a)

did a battery of STS on school children in Central America, then administered extra protein in the diet in the form of a mid-morning "snack" for a year, together with treatment for intestinal parasites At the end of this time they repeated their battery of STS and found no significant change in the percentage of sero-positivity They also estimated serum-levels of carotene, vitamin A, and vitamin E among the children and found a lower level for all three (though not below the limits of normality) among children who gave BFP reactions with lipoidal antigen than among those children who were negative to STS with lipoidal antigen They consider that the lower values are not the cause of the BFP reactions, but that some common factor is the cause of both BFP reaction and low serum levels of carotene, vitamin A, and vitamin E All these are fat soluble factors and must be carried in the blood in relation to serum lipids or lipo-proteins

While the causes of the acute BFP reactions are numerous and well known, the cause of chronic BFP reactions with long duration is less certain Moore and Mohr (1952a, b) mention leprosy as one disease which may cause this type of BFP reaction They also stress that the collagen diseases, such as disseminated lupus erythematosus, periarteritis nodosa, rheumatoid arthritis, rheumatic fever, and sarcoidosis, are common causes of chronic BFP reaction Of particular interest is the fact that the STS may become positive long before the precipitating disease is clinically apparent

In quite a high proportion of cases no cause can be found to account for the BFP reaction Minute amounts of reagin are present in sera from all normal persons, and in a few healthy persons it is present in sufficient amounts to produce positive results in STS (Moore and Mohr, 1952a) Durel, Sausse, and Borel (1952), reporting on their experience using the TPI test in 1,000 cases state that the origin of the BFP reaction was rarely found, most of their patients being healthy at the time and having nothing significant in their histories Nelson (1952), reporting on patients found to have BFP reactions by the TPI test in the United States Navy, could find no known factors responsible for the BFP reactions in 74 per cent of them Wilkinson (1954) could find no cause for the BFP reaction in the majority of his TPI-proven cases Wheeler and others (1954), working with the TPI test, found that, when a specific cause for acute BFP was present in a patient with a positive STS only then 78 per cent were true BFP reactions whereas, when no aetiological condition was found, only 53 per cent were BFP reactions

Incidence of BFP Reactions—The published reports on the incidence of BFP reactions can be divided into those obtained by mass blood testing, and those from clinic, hospital, and problem' patients The latter comprise, of course, a selected group The reports can further be divided into those in which the diagnosis of BFP reaction was confirmed by the use of the TPI test, and those in whom the diagnosis was made solely on clinical, epidemiological, and anamnestic grounds

Of the reports on unselected groups Wolman (1946) studied routine serological tests on 82 070 consecutive maritime entrants from all over the United States Nearly all of them were white but otherwise they were unselected He found an incidence of presumed non syphilitic positives of 1 in 790 (0 13 per cent) Schmidt (1954) reported an incidence of BFP reactions of 0 3 per cent among blood donors in Copenhagen Engle (1941) found the incidence of BFP reactions among 40,545 American college students to be ten (0 024 per cent) Stokes, Boerner, Hitchens, and Nemser (1946) found among 210,261 blood donors in Philadelphia an incidence of BFP reactions of 0 14 per cent In an editorial on BFP reactions (*Lancet*, 1954), it was computed that the proportion of non-treponemal reactions with STS was about 1 in 2,500 (0 04 per cent) Hinton, Stuart, and Grant (1949), using Hinton s own test, reported the results of routine testing on 6,325 prospective blood donors in Massachusetts They estimated the percentage of BFP reactions as 0 2 to 0 3 Thus in presumed non syphilitics in mass surveys the incidence of BFP reactions varies between 0 04 and 0 3 per cent

Among the reports of selected groups, Kahn (1953) states that, in official serological evaluations under the auspices of the United States Health Services, of 2 833 samples tested from non-syphilitic persons (excluding malaria and leprosy) he has not had a single BFP reaction with his test Price (1949), reporting on 8 276 sera tested routinely from a London clinic, found the incidence of BFP reactions to be 0 085 per cent with the Wassermann reaction, and 0 01 per cent with the Price Precipitation reaction Klein and Leiby (1948) found among 3,626 presumed non syphilitics from hospital and unselected groups, that the incidence of BFP reactions was 1 16 per cent with the Kline cardiolipin slide test, and 0 58 per cent with the Kahn test Schmidt (1953) found the incidence of BFP reactions to vary between 0 5 and 0 7 per cent, among 5,250 non syphilitic patients from hospital and antenatal practice Thus the reported incidence of BFP reactions among hospital and clinic patients varies from 0 01 to 1 16 per cent

Stokes and James (1949) state that the proportion of biologic or non specific positives in a series of *routine positives* may approach 40 per cent" Moore and Mohr (1952a), reported on experience with the TPI test that

> In certain population groups in the United States (especially in white persons of relatively high socio-economic state in the North-eastern Northern and North-western states), at least half of the sero positive reactors discovered in mass blood testing programs do not have syphilis at all

Again, Moore and Mohr (1952b) report that of 309 white patients seen in private practice who had persistently positive STS and no other signs symptoms or history suggestive of syphilis 136 (45 per cent) were TPI negative Ledbetter (1954) reported that of 1 933 sera from patients in the United States Navy, submitted for TPI test because the serological result was not in keeping with the clinical findings 42 4 per cent were TPI negative Nelson (1952 1953) reported two series of 529 and 496 patients who were STS-positive but without history signs or symptoms of syphilis Of these 42 per cent and 42 5 per cent respectively were TPI negative Wilkinson (1954) reported an incidence of

29 7 per cent TPI-negative among 209 " problem ' sera submitted to the V D Reference Laboratory, London However, with sera of patients with presumed latent syphilis (positive STS but no other evidence of syphilis) from a London clinic, he found the TPI test negative in 4 8 per cent of 42 untreated cases and 5 5 per cent of ninety treated cases

Wheeler and others (1954) performed the TPI test on 733 sera from individuals who had had at least one, usually two or more positive STS reactions They describe them as patients in whom the clinical and serological findings were such that a definite diagnosis was impossible Of these, 46 1 per cent were TPI-negative They make the further interesting observation that, when a tentative diagnosis had been submitted with the specimen, of 173 TPI-positive sera, only 81 (47 per cent) had been tentatively diagnosed as syphilis, whereas of 199 TPI-negative sera 164 (83 per cent) had been tentatively diagnosed as BFP results These figures illustrate well the increasing tendency to regard as non-specific those positive STS reactions unassociated with obvious evidence of syphilis Thus the reported incidence of false positivity among patients having repeatedly positive STS and no other evidence of syphilis varies between 4 and 46 per cent

The Problem in the Tropics

Most of the work on the incidence and nature of BFP reactions has been done in a temperate climate, with the exception of the intensive study from Central America (Stout and Cutler, 1951 , Stout, Aguirre, and Scrimshaw, 1952 , Stout, Mendez, Guzman, and Scrimshaw, 1952 , Stout, Guzman, and Scrimshaw, 1952a, b , Levitan and others, 1952) It is, however, generally assumed that the incidence of BFP reactions under tropical and sub-tropical conditions will be materially higher than in temperate climates Roy and others (1953) state

> Recognition of biologic flase positive serological tests for syphilis has become of great importance This is true not only in such countries as the United States, but even more in rtopical countries, such as India, in which there are relatively high incidenced of malaria, leprosy, and other diseases in which biologic false positive tests are known to occur

Willcox (1952), discussing the incidence of neurosyphilis in Africans, mentions the frequency of false positive reactions to STS in a malarious country The World Health Organization Sub-Committee on Serology (1950) state

> There is some evidence to support the belief that the prevalence of the disease (syphilis) in some world areas has been greatly exaggerated, being based on the high proportion of positive serological findings It is very possible that this picture is the result of an environmental condition quite distinct from syphilis

Mahoney and Zwally (1949), commenting on the high incidence of positive serological findings which have been reported from some tropical areas, suggest that unrecognized environmental factors may be responsible for a serological picture entirely at variance with the frequency with which syphilis is encountered Levitan and others (1952) make a similar suggestion Unfortunately, the laboratory facilities needed to unravel this problem are most deficient in the very areas where the problem is most pressing Rein (1952), discussing the sero-diagnosis of yaws, commented that " sero-diagnostic facilities were least where yaws is most common " With the general fall in the incidence of syphilis in Europe and the United States of America, the same might now be said of syphilis

With such a wealth of published opinion expressing doubts on the efficiency of STS in the tropics and sub-tropics, it is not surprising that a tendency is growing in Africa to disregard a positive STS result, in the absence of obvious signs of early syphilis, without first attempting to establish the diagnosis on anamnestic and epidemiological grounds and in the light of the results of physical examination Sachs and Selesnick (1953), discussing their experience among Africans in Johannesburg, make the generalization that STS of low titre should not be treated, with the exception of pregnant women Macnab and Murray (1953), commenting on this work of Sachs and Selesnick, state

> Intensive investigation is required into the question whether the Bantu (African) reacts to reptonemata in the same way as the European and, above all, whether the positive serological reactions so frequently found among them can, in the majority of instances, be equated with a treponemal infection

It was in an attempt to investigate the relation of a positive serological reaction to the presence of treponemal infection in Africans that the present investigation was made

Present Investigation

The present investigation is based on the findings in 6,797 successive new adult African patients attending at eight different V D clinics held at regular intervals at scattered points throughout the Eastern Province of Northern Rhodesia during 1953 and the early months of 1954 A routine qualitative Kahn test was performed on each new adult patient, irrespective of the reason for attending the clinic They were also subjected to a physical examination, often under difficult conditions as clinics are held in any building that happens to be available Dark-ground examinations were performed on all patients with primary and secondary syphilis (with very rare exceptions, such as the man with the chancre beneath a phimosed prepuce or

the woman who was menstruating), and smears examined for gonococci from all men with a urethral discharge and from every woman Facilities for performing culture examinations were not available In every case where the Kahn result did not fit in with the clinical findings it was repeated at the next visit (in 1 or 2 weeks), as advised by Rein and Elsberg (1944) In this way it was hoped to eliminate the bulk of technical false positives due to faulty labelling or handling of specimens All specimens were in the refrigerator within 36 hours of being taken and were tested within a further 36 hours None of the specimens was brought more than 150 miles by road

The technique used in the performance of the Kahn test was exactly as described by Kahn (1950d) The antigen used was of several batches obtained from the South African Institute for Medical Research, Johannesburg This antigen was usually excellent, but, on the rare occasions when any doubt was felt about the reliability of a particular batch of antigen, it was tested in parallel with another test (either the Eichorn-Rappaport or Price Precipitation reaction), and if doubt still existed the batch was discarded The standard Kahn test was used in this investigation not because it was felt that it had any special virtue over other tests, but because it is the routine serological test for syphilis most commonly used throughout Central Africa It is felt that, in view of the diverse opinions as to the value of the different tests in common use, there is no justification for changing the test already established Best results will probably be obtained with the test with which a laboratory is most familiar

Of the total of 6,797 patients 791 had to be excluded from the analysis because they failed to attend for repetition of serological tests, because details of history were not recorded, or because for some other reason the diagnosis could not be ascertained Details of the remaining 6,006 patients, together with the results of their Kahn tests are given in Table I For the purposes of this analysis the Kahn results are classified as

(*i*) Positive (+++, ++, +++ or ++ according to Kahn's method of reading),
(*ii*) Weak positive (+ and ±)
(*iii*) Negative

All cases with clinical signs of syphilis, other than in the primary, secondary, and congenital stage, have been classified as late syphilis without reference to stage or system involved It should not be assumed that these figures indicate the relative incidence of early (primary and secondary) syphilis and of late syphilis The average African does not recognize the nature of the late manifestations of syphilis, particularly neurosyphilis and cardiovascular syphilis, and will go to the hospital rather than to the V D clinics Such cases are therefore usually seen at the hospital, and do not pass through the books of the V D clinics The same is true to a lesser extent of congenital syphilis in adults, though late manifestations of congenital syphilis in Africans are rare, as pointed out by Willcox (1949) from Southern Rhodesia

TABLE I
KAHN RESULTS AND SYPHILITIC STATE

Clinical Findings	Positive	Weak Positive	Negative
Primary syphilis	282	229	194
Secondary syphilis	493	18	—
Late syphilis	23	—	—
Congenital syphilis	4	3	1
Other	900	989	2 870
Total (6 006)	1,702 (28 3 per cent)	1 239 (20 6 per cent)	3 065 (51 1 per cent

As is shown in Table I, the results of the Kahn tests in the patients with overt manifestations of syphilis are in complete agreement with the clinical findings Of 705 cases of primary syphilis 40 per cent were positive, 32 per cent weak positive, and 28 per cent negative Of 511 cases of secondary syphilis, 96 per cent were positive, 4 per cent weak positive, and none negative

Of the 3,065 patients with negative Kahn tests, 194 had early primary syphilis, 915 had gonorrhoea, twenty non-specific urethritis, fifteen lymphogranuloma inguinale, ten chancroid, one granuloma venereum, three had a simple balanitis, and 25 gave a definite history of syphilis which had been adequately treated A further 93 patients with negative Kahn tests complained of repeated abortions but had no other history or symptoms suggestive of syphilis In the remaining 1,789 patients with negative Kahn no evidence of any form of venereal infection could be found Quite a number of them were antenatal cases, some came with a variety of skin diseases which they thought might be of venereal origin a very large number came because of dysuria due to bilharzia which they thought was of gonococcal origin and the remainder came to make sure These cases are largely the by product of several years of intensive propaganda as part of the general measures against venereal disease in this area

There remain 1,889 patients (869 men and 1 020 women) who repeatedly gave positive or weak positive Kahn reactions and in whom no overt

signs of syphilis or other treponematosis was found These patients, 31 5 per cent of the total analysed, are of special interest, since any or all of them might be BFP reactors

Nelson, Zheutlin Diesendruck, and Austin (1950) diagnosed latent syphilis on the following criteria

(*i*) history of suggestive early lesions or repeated exposures to cases of early syphilis,

(*ii*) persistently positive STS for several months in the absence of known possible causes of BFP reaction

They excluded late syphilis by the absence of clinical manifestations and the finding of a normal cerebrospinal fluid Their fifty untreated patients conforming to these criteria all gave positive TPI tests

The criteria used here have, of necessity, had to be less stringent for the following reasons

(*a*) Every one of these patients will have had malaria (a known possible cause of BFP reaction), not once but many times

(*b*) It is impossible to estimate which of the patients had been exposed to cases of early syphilis Willcox (1949) has given a very excellent account of the promiscuity of the African in Southern Rhodesia Much the same applies in the Eastern Province of Northern Rhodesia The African Affairs Annual Report for 1953 (Northern Rhodesia, 1954) shows that 1,015 adultery cases and 2,407 divorce cases were heard before the Native Courts in the Eastern Province Of the divorce cases about 70 per cent were for adultery, which makes a total of 2,699 adulteries among 102,901 adult men It is doubtful whether as much as 5 per cent of the actual adulteries that occur ever come to the notice of the Native Courts

(*c*) Lumbar puncture was not performed on these patients At most of the rural clinics where many of these patients were seen, facilities were not available for this examination In any case, experience has shown that, except when he has a well marked neurological lesion, the African is most unwilling to submit to lumbar puncture, and that if the matter is pressed, the patient and most of his friends simply default Kvittingen and others (1952) from India have described what happens when an unpopular measure is pressed among backward peoples

Method of Assessment

In attempting to decide whether or not a persistently positive Kahn reaction was or was not due to syphilis, the following points have been investigated

(*i*) *History* —African memories are admittedly short, but the large majority of Africans can remember the occurrence of genital sores, particularly if they were followed by a few painful injections As to the date of the infection they are often much less certain and the usual answer to this question is last year" or long ago', neither of which has very much relation to the calendar It should be stressed that accurate histories are much more likely to be obtained when the examiner is well known and has been in the district for some years

It has usually been accepted that, where a positive STS reaction is associated with a definite history of syphilis the STS is a true and not a false positive Rein (1952), however, discussing the value of anamnestic evidence in the diagnosis of yaws, suggests that it is fraught with danger, since 'the news soon gets around among the natives that they will receive some 'magic medicine if they say they have had yaws, and this they will gladly do with the hope that it will cure their bone pains and malaise, as well as many imaginary ills' This is a point of very real importance, but it can be discounted in the series under investigation, as it has never been the practice to give treatment on the history of syphilis only

It is true that the genital sores may not have been syphilitic, but the causes of genital sores other than syphilis are rare and it can safely be assumed that the vast majority of patients who gave such a history did in fact have syphilis

(*ii*) *Scars* —Usually in the European the lesions of early syphilis heal without scarring This is not true of Africans, for a variety of reasons De Mello (1948) has given an excellent description of how the typical chancre in Africans becomes secondarily infected with pyogenic organisms Most patients apply various "native medicines' locally to the lesions, whether or not they are having Western medicine at the same time Many of these native medicines are vegetable astringents, and not a few of them include cow-dung among other ingredients It is therefore not surprising that the lesions become secondarily infected and that they heal with a well-marked and often characteristic scar The frequent depigmentation in scars on black skins and the tendency of Africans to ready formation of keloids all add to the ease with which scars of old genital sores may be recognized

Of course, there are many other causes for genital scars, tears in childbirth and infected scabies are two of the more common but the typical regular, depressed, depigmented scar on the external genitals is commonly caused by chancre or chancroid only Stokes and James (1949), discussing the diagnosis of BFP reactions, mention the importance of finding penile scars, but most other writers do not mention it The finding of typical scars in an African with a positive STS reaction is considered a strong indication that the reaction is a true positive It is also strong supporting evidence of a history of syphilis

(*iii*) *Parent of a Congenital Syphilitic* —Zellmann (1954) states that the diagnosis of congenital syphilis in a child is certain evidence of syphilis in the mother In this series, where a child has been found to have congenital syphilis, there has been no hesitation in accepting the parents' positive Kahn result as a true positive

(*iv*) *Partner's Condition* —In the analysis of this series careful note was made of the clinical and serological state of husband and wife (or other sexual partner), when both partners were seen

Where one partner was a case of primary or secondary syphilis, a positive Kahn test in the other partner was accepted without reservation as a true positive

Where one or both of the partners had a history of genital sores and/or genital scars, the finding of positive Kahn tests in both partners was taken as strong confirmatory evidence that both of them were true positives and not BFP reactions

On the other hand, some doubt was felt about assuming when neither partner had history, scars, or other evidence of syphilis, that because both partners had positive Kahn tests these were therefore true positives From a village-to-village survey made in one area of the Eastern Province in 1950–51, it is known that 13 2 per cent of adult Africans have positive or weak positive Kahn tests On the evidence of this figure the chance of a man and woman who both had positive Kahn tests marrying is 1 in 57, which is small However, since knowledge of the causes of BFP reactions in the tropics is so small, and since some of them may be due to dietary or environmental factors which would be likely to be common to both parties after marriage for any length of time, it is considered unjustifiable to assume that such positive Kahn tests are true positives

Cases where one partner was persistently positive to the Kahn test and the other partner persistently negative presented a problem On the face of it one would tend to regard such results as BFP reactions There are, however, certain facets of African life which would predispose to such an occurrence

(*a*) Marriage is often a fairly temporary arrangement The African Affairs Annual Report for 1953 (Northern Rhodesia, 1954) shows that in the Eastern Province with 102,901 men, 2,407 divorce cases were heard before the native courts That is to say each year one man in every 43 obtains a divorce It is thus probable that with a proportion of men the wife with whom he attended the clinic was not his wife at the time when he was in an infectious stage of syphilis In fact, his positive Kahn test was a true positive and his present wife s negative a true negative The practice of polygamy further complicates the issue

(*b*) By custom, an African man will not have intercourse with his wife during the time she is breast-feeding a baby (up to 2 years) This taboo is less widely observed than previously but still holds great sway There is ample time for the husband to acquire syphilis by extra-marital intercourse, and with minimal treatment to reach a non-infectious stage, during the time his wife is breast-feeding her baby The husband would then give a true positive Kahn reaction, and his wife a true negative

(*c*) A good many men from the rural areas go away to the towns to work Most of them go for periods of 2 to 3 years and their wives do not usually accompany them The African Affairs Annual Report for 1953 shows that 38 per cent of the men were away at work outside the province These conditions are ideal for either husband or wife to acquire syphilis independently, and to reach a non-infectious stage by the time the husband returns from work

Therefore, when only one partner gave a repeatedly positive Kahn test in the presence of a definite history and/or genital scars, such a result was still accepted as a probable true positive, even though the other partner gave a repeated negative Kahn test When, however, a partner without history, genital scars or other evidence of syphilis was found to have a positive Kahn reaction, the finding of a negative Kahn reaction in the other partner was taken as further evidence for classifying the first partner's positive as a probable BFP reaction

(i) *History of Repeated Abortions, Miscarriages, and Stillbirths* —Such a history is a well-recognized finding in syphilitic women Kampmeier (1946) states that when syphilis remains untreated, pregnancy terminates in miscarriage or stillbirth in 24 per cent of cases Meyer (1951) found in a slum area of Paris that 11 per cent of women having stillbirths and abortions had a positive Kahn test Laird (1954) reported from Ceylon that in women who were sero-positive there was a higher proportion of foetal loss than in women who were sero negative

In this series there were 107 women who complained of repeated abortions, miscarriages or stillbirths without history, scars, or other evidence of syphilis The Kahn test was positive in only fourteen (13 per cent) of them Such patients have therefore been classified as giving possible BFP reactions Where, however, a positive Kahn reaction was found in a woman with a history and/or other evidence of syphilis, the history of repeated abortions, miscarriages, and stillbirths was taken as further confirmatory evidence for classifying the Kahn result as a probable true positive

(ii) *Other Factors* —Among the 1,889 patients who gave positive or weak positive Kahn tests and showed no signs of syphilis, there were three cases of chancroid 21 of lymphogranuloma inguinale, three of granuloma venereum, and one of leprosy In none of these could any evidence of syphilis, other than the positive Kahn test, be found All of them have been classified as giving probable BFP reactions

It is, of course, difficult to be absolutely certain in chancroid lymphogranuloma inguinale, and granuloma venereum that a syphilitic infection does not co exist Several cases seen with a definite double infection (as shown by positive dark-ground), have been classified under the appropriate stage of syphilis

In the cases of chancroid lymphogranuloma inguinale and granuloma venereum which have been classified as probable BFP reactions, not only was there no evidence of syphilis, but also the lesions healed without the use of antisyphilitic drugs, except in the case of granuloma venereum, where streptomycin was used

In the whole series of 6 006 there was a total of thirteen cases of chancroid (without evidence of concurrent syphilis) Of these, three (23 per cent) gave positive Kahn tests Stokes and others (1944b) state that the occurrence of BFP reactions in chancroid is denied by some, but quote another series of 24 patients in which five gave BFP reactions Moore and Mohr (1952a) give the incidence of BFP reactions in chancroid as 5 per cent

Of 36 cases of lymphogranuloma inguinale (without evidence of concurrent syphilis) 21 (58 per cent) gave positive Kahn reactions Stokes and others (1944b) quote 6 to 36 per cent as the estimated incidence of BFP reactions in this condition Moore and Mohr

(1952a) give 20 per cent Simpson (1954), in a series of 200 cases of lymphogranuloma inguinale among British troops in India, found twelve who had positive STS reactions, of whom six subsequently proved to have syphilis, giving the incidence of BFP reactions in his series as 3 per cent

Of the four cases of granuloma venereum in the series, three gave positive Kahn tests It is extremely difficult to exclude the possibility of previous syphilis in this condition, and no conclusions can be drawn from such small numbers

Results of Assessment

An analysis of the 1,889 patients who gave positive or weak positive Kahn results without any clinical manifestations of active syphilis is given in Table II Without the use of the TPI test or of cerebrospinal fluid examination it is impossible to be entirely accurate in the assessment of these cases For this reason the words " possible " and " probable " have been used in conjunction with the final assessment Using the indications enumerated and discussed above, patients have been assessed as follows

(1) *Probable True Positive Results*—Patients placed in this category had two or more indications of syphilis, besides their serological result The exceptions to this rule were 33 patients in whom the only evidence was that their sexual partner had early infectious syphilis,

TABLE II

ANALYSIS OF 1 889 PATIENTS WHO GAVE REPEATEDLY POSITIVE OR WEAK POSITIVE KAHN TESTS AND HAD NO CLINICAL MANIFESTATIONS OF ACTIVE SYPHILIS

Probable True Positive Results		Possible True Positive Results		Possible BFP Results		Probable BFP Results	
Indications	Number	Indications	Number	Indications	Number	Indications	Number
History scars and partner *S*	180	History only	236	Partner *S* only	146	N A D	143
History scars and abortions	64	Scars only	102	Abortions only	14	Lymphogranuloma inguinale	21
History scars and partner *C*	41	—	—	—	—	Chancroid	3
History partner *S* and abortions	36	—	—	—	—	Granuloma venereum	3
History scars partner *S* and abortions	38	—	—	—	—	Leprosy	1
History scars and baby *C*	14	—	—	—	—	—	—
History partner *S* and baby *C*	2	—	—	—	—	—	—
History scars partner *S* and baby *C*	8	—	—	—	—	—	—
History and scars	316	—	—	—	—	—	—
History and partner *S*	184	—	—	—	—	—	—
History and abortions	64	—	—	—	—	—	—
History and partner *C*	35	—	—	—	—	—	—
History and baby *C*	10	—	—	—	—	—	—
Scars abortions and baby *C*	1	—	—	—	—	—	—
Scars abortions and partner *S*	13	—	—	—	—	—	—
Scars and partner *S*	95	—	—	—	—	—	—
Scars and abortions	23	—	—	—	—	—	—
Scars and partner *C*	36	—	—	—	—	—	—
Scars and baby *C*	6	—	—	—	—	—	—
Partner *S* and abortions	15	—	—	—	—	—	—
Partner *C* only	33	—	—	—	—	—	—
Abortions and baby *C*	1	—	—	—	—	—	—
Baby *C* only	5	—	—	—	—	—	—
Total	1 220	—	338	—	160	—	171

History Patient with a definite history of genital sores
Scars Patient with typical scars of healed syphilitic lesions on genitalia
Abortions Patient with history of repeated abortions miscarriages or stillbirths
N A D Patient who has no history signs symptoms or epidemiological evidence of syphilis
Partner *S* Patient whose sexual partner also has a positive Kahn test
Partner *C* Patient whose sexual partner has early infectious syphilis
Baby *C* Patient whose child has congenital syphilis

(*i*) Kolmer 51 0 per cent positive,
(*ii*) Kolmer Cardiolipin 18 3 per cent positive,
(*iii*) Kline Standard 22 3 per cent positive,
(*iv*) Kahn Standard 82 3 per cent positive,
(*v*) VDRL Slide Test 3 8 per cent positive

Thus the lowest incidence of BFP reactions was with cardiolipin antigens, and they further noted that using lipoidal antigen in quantitative tests quite a number gave high titre results, whereas, using cardiolipin antigen, titres were much lower They also state that *Plasmodium falciparum* infections are less likely to cause BFP reactions than *Plasmodium vivax* infections

(*b*) *Naturally Acquired Malaria*—Singh (1947) performed STS on patients with malaria in hospital in India Tests used were the Wassermann and the Kahn, and he found positive results in 38 6 per cent Since 11 3 per cent of the non malaria patients in the hospital had positive STS results he gave the incidence of BFP reactions in malaria as 27 3 per cent He could find no relation between the occurrence of BFP reactions and either the patient's temperature at the time of taking the specimens, or the type of the malaria parasite Wilson and Levin (1936) studied BFP reactions among malaria patients in South Carolina Excluding all patients with any suggestion of syphilis they found that 6 3 per cent of 263 patients gave BFP reactions About one-third of them were *Plasmodium falciparum* infections, but they gave no comparison between the incidence of BFP reactions in the different types of infection They also reported one case in which malaria apparently caused a BFP reaction in the cerebrospinal fluid Rein and Elsberg (1944) reported a small series of malarial patients (non-syphilitic and sero-negative before the attack) and found 44 per cent developed a BFP reaction between the seventh and fourteenth day following the first paroxysm Robinson and McKinney (1945) studied 100 non-syphilitic soldiers who had recently been transferred from a malarial area, and who had *Plasmodium vivax* in the blood smear They did blood Kahn tests on them and examined their cerebrospinal fluids (Kahn test Pandy test, and cell count) The results of the cerebrospinal fluids were all normal, except that in two of them the Pandy test was reported as a trace Of the Kahn tests done on their bloods, 33 per cent were positive and a further 11 per cent doubtful On weekly testing they found that 83 8 per cent of the positives and 70 per cent of the doubtfuls were negative within 4 weeks, and all cases were negative after 11 weeks

Manson-Bahr (1945a) states about 28 per cent of malarial bloods in the acute stages of malaria when parasites are plentiful in the peripheral blood, give a positive Wassermann reaction He quotes the results of Wassermann reactions performed on 246 malarial patients as follows

(*i*) *Plasmodium falciparum* 8 2 per cent positive,
(*ii*) *Plasmodium vivax* 11 8 per cent positive,
(*iii*) *Plasmodium malariae* 20 5 per cent positive

Taussig and Orgel (1937) reported the results of Kahn tests performed on 154 non syphilitic patients in St Louis Nearly all of them were *Plasmodium vivax* infections They found that 21 per cent gave positive Kahn tests and observed that, in those whom they followed up the Kahn test became negative within 15 days of quinine therapy Andujar and others (1948) found two patients with positive Kahn tests and five doubtful Kahn tests out of 24 cases of malaria (chiefly *Plasmodium vivax*) giving a total of 29 per cent Cumming, Hazen Sanford Senear, Simpson and Vonderlehr (1935) reported that of a total of 35 malaria patients, four (8 6 per cent) gave positive Kahn results However, when they used a battery of tests, the incidence rose to 20 6 per cent Willcox (1949) reported the results of Kahn tests done on 112 Africans with malaria in Southern Rhodesia He did not mention the type of infection, but the vast majority would almost certainly be *Plasmodium falciparum* He found 9 8 per cent Kahn positive and a further 15 2 per cent Kahn doubtful (total 25 per cent) Nelson (1947) performed a battery of STS on 100 European Service personnel with acute *Plasmodium falciparum* malaria on the Gold Coast He did STS within 24 hours of the onset of parasitaemia and again on the tenth day, and found an incidence of positive results of 3 per cent (Ide test, 2 per cent Meinicke test, 4 per cent and Kahn test 3 per cent)

Thus, in the reports quoted above, the incidence of BFP reactions in induced malaria varied between 100 and 3 8 per cent depending on the tests used and in naturally acquired malaria between 44 and 2 per cent

Present Investigation

In an attempt to elucidate the part played by malaria in causing BFP reactions in the Eastern Province of Northern Rhodesia, Kahn tests were performed on a series of African patients with positive blood slides for malaria at the African Hospital Fort Jameson A total of 137 patients were so examined and 38 (27 7 per cent) were found to give positive or weak positive Kahn results It was not found possible to examine these patients for syphilis since usually by the time the Kahn test result was available, the patient had had his anti malarial treatment and had ceased to attend the African Hospital The only criterion for inclusion in this series was that the patient should have a malarial parasitaemia (*Plasmodium falciparum*) in all cases and that the laboratory assistant could find time from his other duties to track down the patient after he had read the blood smear and take the blood sample for Kahn testing A brief note however was made on each patient giving his approximate age and whether or not he had fever at the time of taking the blood specimen for the Kahn test

The majority of the positive patients (79 per cent) were in the weak-positive range (Table IV, opposite) It will be seen that the incidence of positive results is much higher among children than among adults Of 97 adults 23 (23 7 per cent) gave a positive Kahn result whereas of the forty children fifteen (37 5 per cent) gave positive Kahn results There appears to be no relation between the occurrence of positive Kahn results and the presence or absence of fever at the time the specimen was taken

Stokes and others (1946) in Philadelphia were able to show a degree of parallelism between the monthly

incidence of BFP reactions and the monthly incidence of pneumonia In an attempt to assess the importance of malaria as a cause of BFP reactions further analysis of the 6,006 patients, described earlier, has been undertaken The percentage of patients classified as N A D (no history, signs, symptoms, or epidemiological evidence of syphilis, but showing a repeatedly positive Kahn test) has been worked out for each month An indication of the monthly variation in the incidence of malaria has been obtained from the number of patients found

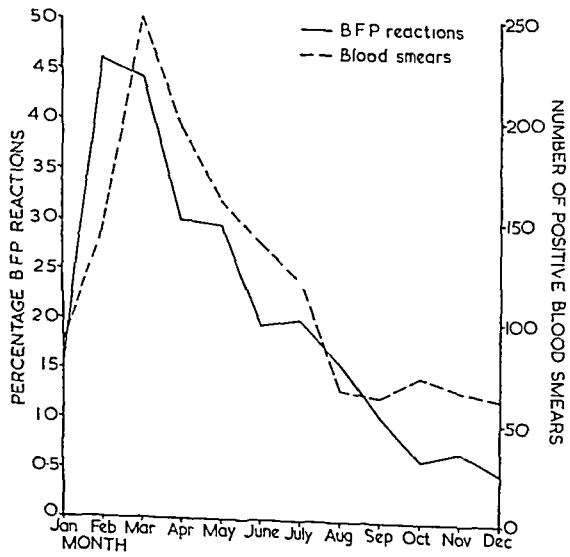
TABLE IV
KAHN RESULTS IN PATIENTS WITH MALARIA

Kahn Result	Adults		Children	
	Fever	No Fever	Fever	No Fever
Positive	3	1	4	—
Weak positive	14	5	11	—
Negative	58	16	22	3
Total	75	22	37	3

to have positive malaria blood smears at the African Hospital, Fort Jameson, for each month during 1954 There is close parallelism between the monthly variations of the incidence of BFP reactions and of malaria throughout the year (see Figure below)

Discussion

From the results described above it is apparent that a greater percentage of positive Kahn results occurred in Africans with malaria than in the general population The village-to-village survey carried out in 1950–51 showed that 13 2 per cent of the adult population had positive Kahn tests,



FIGURE—Monthly percentage incidence of BFP reactions and monthly number of positive blood smears for malaria for 1954

whereas among the adults with malaria 23 7 per cent had positive Kahn tests—an increase of 10 5 per cent It is more than likely that, had serial testing been carried out on the patients, a higher percentage of positives would have been found, but it seems unlikely that this would have reached the high percentage described in experimentally inoculated malaria

There is one obvious difference between the healthy American prison inmate inoculated with malaria, and the African in his village bitten by an infected mosquito , that is, for the American it is probably his first attack of malaria, whereas for the African it is only the latest in a long series Rein and Kent (1947), reporting their study on penitentiary inmates inoculated with malaria, noted that, " the incidence of false positive reactions appears highest in early primary malaria, somewhat lower in delayed primary attacks, and lowest in relapses This would seem to indicate that the body responds to the repeated assaults of malaria by producing less and less reagin Repeated attacks, such as are the lot of the African living in an area of endemic malaria, would therefore tend to produce relatively few BFP reactions Possibly racial and acquired immunity to malaria would also play some part in this mechanism

Further support to this supposition is given by the high incidence of positive Kahn tests found among children with malaria Admittedly the numbers are small, but the finding of a positivity rate among the children of 37 5 per cent as compared with 23 7 per cent among adults requires some explanation It can be assumed that the children would, generally, have had far fewer attacks of malaria than the adults, and would therefore be more likely to respond to an attack of malaria by producing a BFP reaction Scrutiny of the Kahn results among the malarial children shows a tendency for more positives to occur among the younger age groups This is in keeping with the report by Smith (1950) from an area of Northern Rhodesia that over the age of 1 year the spleen rate (on which he judged the incidence of malaria) tended to diminish with rising age Laurie (1954), working on Ukara Island in Lake Victoria, found in a random group, from whom blood films were examined for malaria, that the incidence of positive films fell as age increased He also found that, while the adult population gave 14 to 16 per cent positive Kahn tests, 13 per cent of the children also gave positive results, possibly caused by malaria

It is, of course, possible that the positive Kahn tests found among children are due to a form of endemic syphilis or to congenital syphilis However,

since congenital syphilis, though commonly seen in Africans in the first year or two of life, is rarely encountered later, and since no cases suggestive of endemic syphilis have been seen, this possibility seems remote Furthermore, Guthe and Reynolds (1951), reporting on endemic syphilis in Bosnia noted that the sero-positivity rate rose from 0 6 per cent in the 0 to 5 years age group to 13 4 per cent in the 16 to 18 years age group, whereas in the series reported here the highest incidence of sero-positivity was in the younger children

That malaria is a cause of BFP reactions in the Eastern Province of Northern Rhodesia cannot be doubted The higher percentage of positive Kahn results among adults with malaria as compared with the general adult population, and the parallelism observed between the monthly incidence of malaria and BFP reactions, are both indications that malaria plays a definite part in the occurrence of BFP reactions The only surprising factor is that, in an area where the population is frequently subjected to the assaults of malaria from birth, the BFP reactions are not very much higher (2 8 to 5 5 per cent in the series of 6,006 described above) The well recognized tendency for *Plasmodium falciparum* infections to cause fewer BFP reactions than other types may explain in part the low figures The supposition that the repeated attacks of malaria may have a diminishing effect in evoking BFP reactions would further explain the findings

Leprosy and BFP Reactions

From the early days of serological tests for syphilis, leprosy has been recognized as causing false positive reactions Badger (1931), in a review of the literature noted very diverse opinions as to the incidence of BFP reactions in leprosy Beerman (1945) in a more recent review, also noted similar wide variation in the reported incidence, but found that the trend was generally towards a high percentage Manson-Bahr (1945b) points out that leprosy and syphilis often co exist He states that,

> In mild early cases of leprosy positive [Wassermann] reactions denote coincident spirochaetal infection but in advanced cutaneous and neural cases, especially those subject to lepra fever, a positive reaction does not necessarily always indicate a syphilitic infection

Moore and Mohr (1952a) state that the BFP reaction associated with leprosy is of the chronic type wherein positivity persists for months or years Kahn (1950b, 1954) described with his universal serological reaction, a typical serological pattern in lepromatous leprosy which tended to move out of the diagnostic range with improvement in the leprosy He mentions however, that this typical pattern is often absent, and postulates that it may often be masked by the effect of intercurrent diseases so often found in leprosy He also states that sero-diagnostic tests for syphilis are commonly negative in tuberculoid and non characteristic forms of leprosy Davis (1944) suggested that the increasing percentage of STS positivity among lepers may be attributed to the increasing sensitivity of modern STS

Badger (1931), who reported on 207 lepers in Honolulu found 20 2 per cent positive with Wassermann and 27 5 per cent with Kahn One or both tests were positive in 28 9 per cent When the tests were repeated one to three times at intervals, the percentage positive rose to 34 8 The incidence of sero positivity in lepers was three times as great as among the general population Positive results were found more often under than over 20 years of age He also noted that a marked clinical improvement was often accompanied by a return to sero negativity, that clinical fluctuation was often accompanied by serological fluctuation and that leprous reactions were often accompanied by a change from sero-negative to sero positive Correlation between clinical state and strength of quantitative Kahn result was also noted He found no difference in incidence of sero positivity between dermal and neural types

In a review of serological techniques in the United States Cumming and others (1935) reported performing STS on fifty cases of leprosy and found thirty were positive and one doubtful with the Kahn test (62 per cent) Positive results obtained with different tests on these fifty lepers varied between 42 and 76 per cent Rein and Elsberg (1944) found 85 per cent among eighty lepers positive to a battery of STS Kolmer and Lynch (1953) state that in leprosy single tests may only give 15 to 20 per cent false positive reactions, whereas incidence based on repeated tests may be 60 per cent or higher Moore and Mohr (1952a) give the incidence of BFP reactions in leprosy as 60 per cent Singh (1949) reporting on Kahn tests done on 64 non syphilitic lepers in India found that 26 5 per cent gave strong positive and a further 15 6 per cent gave weak positive results (42 1 per cent) In lepromatous cases 35 4 per cent gave strong positive and 22 2 per cent weak positive results whereas in neural types 5 2 per cent gave strong positives and there were no weak positives He also observed, using quantitative tests, that leprosy caused BFP reactions of higher titre than he usually found from other causes (malaria post-vaccination etc)

Nelson (1952) examined seventy apparently non syphilitic lepers of whom 57 (80 1 per cent) gave positive results with various STS Of the 57 showing positive results, eleven gave a positive TPI test thus making the incidence of BFP reactions in leprosy 66 6 per cent Portnoy Ramiro Galvez and Cutler (1952) examined 51 non syphilitic lepers in Guatemala with a battery of STS and found the incidence of BFP reactions to be

(*i*) Kahn 54 9 per cent
(*ii*) Kolmer 22 7 per cent
(*iii*) Kolmer Cardiolipin 30 9 per cent
(*iv*) VDRL 29 2 per cent
(*v*) Mazzini 58 8 per cent

They found cutaneous leprosy gave a higher percentage of positives than neural leprosy Willcox (1949) performed the Kahn test on 829 lepers in Southern Rhodesia and found 16 0 per cent positive and 11 8 per cent doubtful (total 27 8 per cent) Stokes and others

(1944b) quote the incidence of BFP reactions in leprosy as 60 to 80 per cent

Thus, from the reports mentioned above, the published incidence of BFP reactions in leprosy varies between 20 and 85 per cent

Present Investigations

Kahn tests were performed on 477 leper patients in two leper colonies (Nsadzu Mission Leper Colony and Mwami Mission Leper Colony) Of these, 21 (4 4 per cent) gave positive results, and a further 67 (14 per cent) gave weak positive results (total 18 4 per cent) Patients with syphilis were excluded as far as possible

It was noticed that positive Kahn results were much commoner among the female lepers than among the males Of 243 female lepers, 15 (6 1 per cent) gave positive Kahn results and a further 45 (18 5 per cent) gave weak positives, giving a total of 24 6 per cent Of the 234 male lepers, however, only six (2 6 per cent) gave positive Kahn results, and 22 (9 4 per cent) weak positive ones making a total of only 12 per cent

In 408 of the leper patients the predominant type of leprosy at the time of the Kahn test was recorded In many cases a mixed type existed, *e g*, predominantly lepromatous but with a polyneuritic element Positive results were commoner in lepromatous cases than in polyneuritic, and least common in tuberculoid ones (Table V)

TABLE V

TYPE OF LEPROSY AND KAHN POSITIVITY

Type of Case	Total Number of Cases	Number Kahn Positive	Percentage Kahn Positive
Lepromatous	250	53	21 2
Polyneuritic	86	10	14 8
Tuberculoid	69	6	8 1
Intermediate	3	—	—
Total	408	69	—

In 210 patients the bacteriological status of the leprosy when the Kahn test was performed was recorded No correlation between the bacteriological status and the Kahn result was observed Of 69 patients who were bacteriologically positive, eleven (15 9 per cent) were Kahn positive, and of 141 who were bacteriologically negative, 21 (14 9 per cent) were Kahn positive

Patients in this series had been under treatment from 1 month to 25 years In 233 of the patients the length of treatment was compared with the percentage giving positive Kahn results (Table VI) No correlation could be found between these two factors The impression was gained that positive Kahn results tended to go hand-in-hand with the activity of leprosy This is difficult to show statistically However, 234 cases were analysed into first, second, and third stage according to the activity of leprosy at the time of performing the Kahn test Of 68 cases in the third stage and 67 in the second stage, 19 1 per cent and 25 4 per cent gave positive Kahn results respectively, whereas of 99 in the first stage, only three (3 per cent) were positive

TABLE VI

LENGTH OF LEPROSY TREATMENT AND KAHN RESULT

Kahn Test	0–3 Months	3–6 Months	6 Months–1 Year	1–3 Years	Over 3 Years
Negative	37	25	45	35	49
Positive	7	7	8	10	10
Positive %	15 9	21 9	15 1	22 2	16 9

Discussion

The incidence of positive Kahn results among the leper patients here recorded (18 4 per cent) is lower than that in most reported series This may possibly be due to a preponderance of cases in whom the activity of the disease was low when the tests were taken The published reports quoted above give no indication of the activity of the disease when the STS were performed If, as seems probable, sero-positivity is to some extent related to the activity of the leprosy, then the number of BFP reactions in any given series will vary directly with the number of patients in the more active stages of the disease

In the discussion of BFP reactions in malaria, it was suggested that the percentage incidence could be found by subtracting the percentage incidence of positive Kahn results in the adult population of the Eastern Province of Northern Rhodesia from the percentage incidence of positive Kahn results in adults with malaria A similar method of estimating the incidence of BFP reactions in leprosy would not however be valid, for the following reasons ,

(*i*) While the majority of patients in the two leper colonies come from the Eastern Province, a large minority come from other provinces, or from Nyasaland or Portugese East Africa, areas where the prevalence of sero-positivity may be, and in some cases is known to be, markedly different from that in the Eastern Province

(*ii*) The figure available for the incidence of sero-positivity in the Eastern Province applies only to adults, whereas the figures obtained from the leper colonies include quite a number of children

(*iii*) The inmates of the two leper colonies receive a diet which is better than that enjoyed by the average African feeding himself Many of the lepers examined have been inmates of the colonies for considerable periods If, as has been suggested, dietary variations play some part in causing BFP reactions, then the better diet in a leper colony might well play some part in increasing or decreasing the incidence of BFP reactions

The finding that positive Kahn results were twice as common in female as in male lepers was noted with interest Scrutiny of the individual case records failed to reveal a higher proportion of female lepers in the more active stages Badger (1931) made a similar observation

The finding that lepromatous leprosy is more